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Plasticity of lower limb motor axons after cervical cord injury

Robert A. Boland [a], Hugh Bostock [b], Matthew C. Kiernan [a,c,*]

[a] Spinal Injuries Research Centre, Prince of Wales Medical Research Institute, Randwick, NSW, Australia
[b] Sobell Department of Motor Neuroscience and Movement Disorders, Institute of Neurology, University College London, London, United Kingdom
[c] Prince of Wales Clinical School, University of New South Wales, Randwick, NSW 2031, Australia

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ABSTRACT

Objective: To assess changes in peripheral motor excitability after traumatic spinal cord injury (SCI).
Methods: Conventional nerve conduction and nerve excitability studies were longitudinally investigated in a patient diagnosed as C6 American Spinal Injury Association (ASIA) C incomplete. Recordings were undertaken from the peroneal nerve to tibialis anterior, and the median nerve to abductor pollicus brevis throughout the period of hospital admission.
Results: Recordings were acutely abnormal in common peroneal axons 6 days after injury. Threshold electrotonus was "fanned in"; during the recovery cycle superexcitability was abolished, and refractoriness at 2.5 ms was increased (patient 152.84%; controls 37.13 ± 3.83%). All parameters recovered briefly after surgical stabilization on day 9, before regressing by day 13. Excitability values recovered by day 68 when the patient was discharged ambulant as ASIA D. Recordings remained relatively unaffected in median axons throughout the admission period.
Conclusions: Decentralisation after SCI had significant effects on lower limb axons, not attributable to direct trauma. Conversely, median axons remained spared. Modeling of the lower limb excitability changes suggested that interruption of energy-dependent processes contributed to the peripheral abnormalities, perhaps through involvement of upstream transynaptic processes.
Significance: These findings may suggest the potential for plasticity of peripheral axonal excitability in response to acute SCI.

1. Introduction

Despite observations of reduced amplitudes of compound muscle action potentials (CMAPs) and altered H-reflexes after spinal cord injury (SCI) (Hiersemenzel et al., 2000; Nogajski et al., 2006) the prevailing view remains that lower motor neurons remain relatively intact after SCI. Reduced peripheral excitability, reflected by hyporeflexia and weakness (Ditunno et al., 2004), has instead been attributed to changes in descending excitatory and inhibitory inputs, with consequent effects on trophic inputs to the anterior horn cell (Kirshblum et al., 2001). A recent cross-sectional investigation of patients with sub-acute and chronic SCI however, demonstrated altered excitability properties and dysfunction of peripheral motor axons. These were attributed to effects from a combination of decentralization and inactivity (Lin et al., 2007), but the relationship of such changes to insult and recovery could not be defined.

The implication of changes in peripheral nerve excitability for management of SCI are profound. Currently, the aims of medical management during the acute phase after SCI are to stabilise the patient. Rehabilitation issues remain secondary until the patient is medically stable. In the meantime, however, patient outcomes including final functional status and length of admission may be adversely affected if peripheral dysfunction superimposes on effects of cord trauma. To explore this latter possibility, this study utilized combinations of clinical assessment, traditional nerve conduction studies, and novel nerve excitability techniques to evaluate the onset and progression of axonal changes in a patient after traumatic SCI, from the period of spinal shock (that included spinal stabilization surgery), until the patient was discharged from hospital ambulant on day 68.

2. Methods

2.1. Case history

A 31-year-old male sustained a hyperflexion-induced C6 fracture-dislocation as a result of a diving accident and was flaccid upon admission to an intensive care unit (day 0). He remained

* Corresponding author. Address: Prince of Wales Medical Research Institute, University of New South Wales, High St., Randwick, NSW 2031, Australia. Tel.: +61 2 9382 2422; fax: +61 2 9382 2437.
E-mail address: M.Kiernan@unsw.edu.au (M.C. Kiernan).

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haemodynamically stable with normal oxygen saturation, despite transient and minor bradycardia (44–50 beats/min). Magnetic resonance imaging demonstrated fractures of the posterior elements of C5, forward subluxation of C5 relative to C6, and a cord contusion with small haematoma adjacent to the C4/5 disc (Fig. 1). Computed tomography revealed no cerebral or spinal injuries elsewhere.

On examination, motor function graded using the American Spinal Injury Association (ASIA) scale (Marino et al., 2003) was 5/25 for the right upper limb and 3/25 for the right lower limb; 4/25 for the left upper limb and 15/25 for the left lower limb. In particular, left tibialis anterior (TA) and right abductor pollicis brevis (APB) were assessed as 4 and 0, respectively, using grades between 0 (total paralysis) and 5 (normal contraction against examiner resistance) (Marino et al., 2003). Sensory scores were 8/50 bilaterally. Knee jerk was present on the left but absent on the right. Ankle jerks were bilaterally absent. Anal sensation and voluntary contraction were preserved. The diagnosis was C5 ASIA C incomplete tetraplegic, defining SCI with retention of voluntary anal sphincter control, and sparing of motor function more than three levels below the motor level of injury (Marino et al., 2003).

The patient was initially immobilised in halo-cervical traction while he considered whether to undergo surgical stabilisation intervention. Subsequently, he underwent anterior fusion between C5 and C6 on day 9. On day 5, he gave consent for the present series of investigations that were approved by the Human Research Ethics Committees of the South-Eastern Sydney Area Health Service, and the University of NSW.

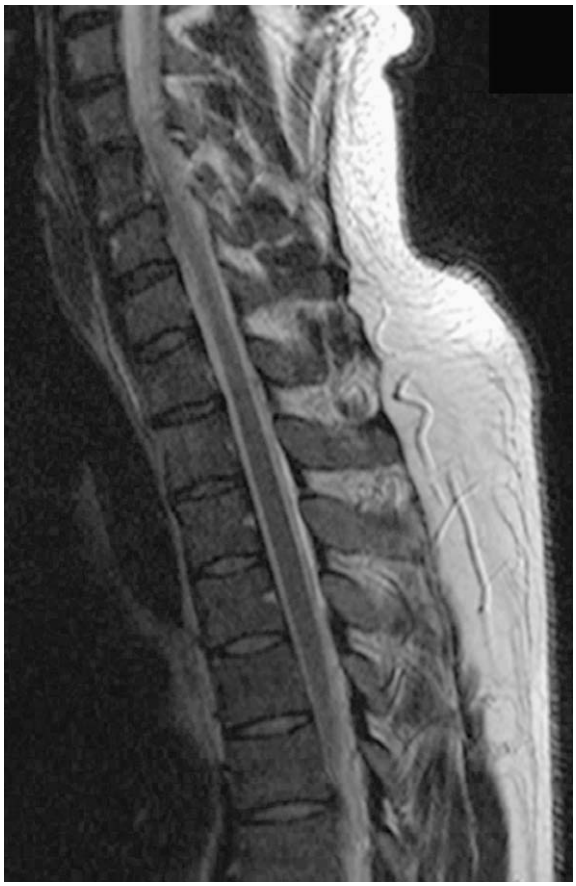

Fig. 1. Sagittal T2 MRI of cervical spine demonstrating site of lesion at C5/C6 with evidence of cord contusion.

2.2. Neurophysiological and clinical studies

Nerve excitability (Bostock et al., 1998) and conventional nerve conduction studies (NCS) were undertaken on the

(i) left common peroneal nerve (CPN) at the head of fibula with the resultant CMAP recorded from TA;
(ii) right median nerve (MN) at the wrist with the resultant CMAP recorded from APB.

In addition, NCS were undertaken on the right common peroneal nerve during the acute period. Excitability data were collected as previously described using QTRAC software (© Institute of Neurology, UK) for stimulus–response behaviour, strength duration time constant, threshold electrotonus, a current–threshold relationship, and the recovery cycle of excitability (Kiernan et al., 2000). Recordings were undertaken on days 6 (before surgery on day 9), 11, and 13. Subsequent recordings were followed longitudinally until day 68, and compared to normative data for MN stimulation (Kiernan et al., 2000; Krishnan et al., 2004) and CPN stimulation (Krishnan et al., 2004). To verify reproducibility of recordings, supplementary test–retest data were collected from 12 healthy control subjects for the MN and CPN at intervals of between 2 and 3 days.

Nerve conduction studies were undertaken using standard techniques (Kimura, 2001) with a Medelec Synergy TECA machine (Oxford Instruments, UK) to determine acute effects on motor conduction parameters. Skin temperature was maintained above 30 °C. Bipolar surface recording electrodes were used with an inter-electrode distance of 4 cm (Eduardo and Burke, 1988). Motor stimulation was delivered to distal and proximal sites at 1 Hz using square-wave pulses of 0.1 ms duration. Filter settings of 20 Hz–2 kHz were used for recordings. To assess recovery, clinical strength assessments, and electromyography recordings from APB and TA, using concentric needles, were also undertaken. To assess for metabolic effects on nerve function, serum electrolyte levels and hemodynamic parameters were evaluated throughout the period of hospital admission.

2.3. Mathematical model of nerve excitability

To clarify the excitability changes in human motor axons that develop following spinal cord injury, mathematical simulations were undertaken using a model of the human axon specifically developed for the peroneal nerve (Bostock et al., 1991, 1995; Kiernan et al., 2005a,b). Transient Na^+ channels were modeled using the voltage clamp data (Schwarz et al., 1995), and persistent Na^+ currents were added (Bostock and Rothwell, 1997) as in previous models (Kiernan et al., 2005a,b). The equations for a single node and internode, representing a spatially uniform axon, were evaluated by integration over successive small time steps (Van Euler's method; Press et al., 1992). The excitability of the model nerve was then tested repeatedly to determine threshold, with an accuracy of 0.5%. The discrepancy between the thresholds determined for the model and those determined from a sample of real nerves was scored as the weighted sum of the error terms (see Kiernan et al., 2005a,b). The weights were the same for all threshold measurements and gave an equal total weight to the different types of threshold measurement, namely the current–threshold relationship, threshold electrotonus and recovery cycle. The standard model was obtained by minimizing the discrepancy between the model and the normal control data with an iterative least squares procedure, so that alteration of any of the above parameters would make the discrepancy worse.