Spinal Cord Function and Rehabilitation – an Overview

This issue of The Journal includes a series of reviews that follow from *The Journal of Physiology* Symposium 'Spinal Cord Function and Rehabilitation' held at the Society for Neuroscience 30th Annual Meeting in New Orleans in November 2000. The symposium was held in honour of Elzbieta Jankowska, a leader in spinal cord research for over 30 years. Our aim is to bring together four groups of researchers who work on spinal cord networks, pharmacology, repair and rehabilitation. With the growing realisation that regeneration of spinal pathways still faces many hurdles, it seems crucial that these groups compare notes and discuss future strategies.

The symposium commenced with a tribute to Dr Jankowska, in which her many important contributions to spinal cord physiology were recognised. She was presented with an original reprint of one of the first papers on reciprocal inhibition (Sherrington, 1893).

Basic spinal cord mechanisms

The spinal cord not only mediates simple reflexes such as the tendon jerk but also generates coordinated sequences of movements. A recurring theme of the first session was the great versatility of *interneurons*. Jankowska reviewed the criteria for classifying interneurons and listed the well-recognised types such as Renshaw cells, as well as interneurons with a more tentative status. She summarised the ways interneurons can operate: combining into networks, shifting the balance of neuronal activity and selecting between pathways. She also reviewed the actions of neuromodulators, showing how they could differentially affect segmental and ascending pathways and influence interneurons by activating plateau potentials.

Hans Hultborn, co-discoverer of plateau potentials in motoneurons, expanded on these themes. He gave examples of temporary groupings of interneurons into 'functional units' controlling tasks such as standing, locomotion and paw-shakes. Dramatic evidence of task-dependent groupings was afforded by the switch from Ib homonymous inhibition in static posture to net excitation during locomotion. Interestingly, Hultborn argued against the term 'phase-dependent reflex reversal' for this switch.

The roles of group I and II afferents in phase-switching and load-compensation were further elaborated by David McCrea. Surveying recent research, he argued that the timing and force of muscle contractions are under moment-to-moment control throughout the step cycle. Reflexes are reorganised so that those operating at rest are suppressed and previously unrecognised types of interneurons are recruited to produce opposite actions during locomotion.

Sten Grillner focused on the cell membrane. He argued that in all vertebrates the spinal cord produces the basic coordinated pattern of locomotion whether in swimming, walking or flying. Ionic mechanisms were at the heart of rhythmogenesis. Various subtypes of calcium and potassium channels were involved, as demonstrated in a remarkable sequence of calcium-sensitive images of a single dendrite during fictive locomotion. Grillner concluded by summarising the sequence of channel activations controlling the lamprey locomotor cycle.

Steven Edgley pointed out that interneurons are given 'nicknames' according to responses to test inputs. However, interneurons receive many diverse inputs. The nicknames may thus highlight one role, but disguise others. Do interneurons with the same nickname form homogeneous groups? Edgley argued that when inputs to interneurons of a given type were randomly distributed, this militated against the existence of subtypes. He echoed Hultborn's concept of *functional groups* in a discussion of the concept of spinal cord 'modules.'

In discussion, Eberhard Fetz reported that during alternating wrist movements in monkeys performing tracking tasks, cervical interneurons most often fired bidirectionally, or had broad directional tuning curves (Fetz *et al.* 1999; Perlmutter *et al.* 2000), in contrast to corticomotoneuronal cells and α-motoneurons which are more tightly directionally tuned. On the other hand, in delayed-onset tasks, many interneurons showed preparatory activity prior to muscle activation, much like cortical neurons. Fetz suggested that movement preparation may occur simultaneously over widely distributed regions, including the spinal cord, but that a global inhibitory mechanism suppressed the expression of such activity in α-motoneurons.

Susan Shefchyk concluded the session with an excellent account of the neural networks that coordinate the bladder and external urethral sphincter. She showed how theories of micturition control had shifted from a purely spino-bulbo-spinal reflex to the inclusion of spinal mechanisms. The future challenge was to understand the details of connectivity, transmitter action and plasticity in these circuits.

Spinal cord plasticity

Next, the focus shifted to clinically related themes. Serge Rossignol reviewed the effects of systemic or intrathecal delivery of neurotransmitters on locomotion before and after spinalisation. Given the importance of maximising locomotor recovery after human spinal cord injury (SCI), it is crucial to know how these neurotransmitters operate

and how they can be manipulated pharmacologically. Rossignol showed remarkable videos of locomotion in spinalised cats and rats after drug applications. The salient neurochemical difference after spinalisation was a dominance of glutamatergic mechanisms. The upper lumbar segments seemed critical for generating locomotion. In discussion, a video was shown of locomotor recovery in rats in which serotonergic cells from embryonic raphe nuclei had been grafted caudal to a spinal transection performed several weeks earlier (Slawinska *et al.* 2000).

Keir Pearson found the evidence that regenerating descending pathways were directly responsible for locomotor improvements after SCI somewhat inconclusive and asked whether enhanced local reflexes might be responsible. He suggested that plasticity in reflex pathways could be used clinically to augment reflexes that facilitated weight support and controlled the timing of the step cycle.

Several guiding principles for exercise training after SCI were proposed by Reggie Edgerton. SCI results in 'a new spinal cord' with altered synaptic function and neurotransmitter expression. Repeated exposure to sensory input and interneuronal activity associated with locomotion may reverse these deleterious alterations, as evidenced in the human case studies presented. Edgerton also showed that upregulation of inhibitory transmitters after SCI in rats and cats could be reversed by exercise training. A future option is to use robots to automate rehabilitative training.

Spinal cord regeneration

Mary Bunge (Jones *et al.* this issue) summarised developments in neural regeneration studies. She discussed various approaches including Schwann cell grafts into SCI sites to provide bridges for axonal growth. Combining neuroprotective steroids and neurotrophins with grafts further enhanced axonal growth. In addition, gene transfer caudal to a graft promoted functional connections of regenerating axons.

The role of neurotrophins, particularly NT-3, was further addressed by Lorne Mendell, who showed that they not only promoted axonal growth, but also modulated the functional capacity of the muscle spindle/motoneuronal connection after peripheral nerve injury and during development. He cautioned that though neurotrophins could enhance functional recovery they also had the potential for producing undesirable effects such as pain and spasticity.

Spinal cord microstimulation

The next three presentations are represented in one review. Arthur Prochazka reviewed the pros and cons of existing neuroprostheses. Surface stimulators are in widespread use to reduce spasticity and pain and to 'retrain' the motor system after SCI. Over 50 000 neuroprostheses, mainly cochlear stimulators and sacral root stimulators, have been implanted in people. *Motor* neuroprostheses are limited in the functions they can restore, but promising new strategies are on the horizon.

One such strategy, intraspinal microstimulation, was presented by Vivian Mushahwar. She described how single muscles or small groups of synergists could be controlled via microwire arrays implanted in the ventral horn. Innocuous stimulation through single wires could sometimes elicit whole-limb activation sufficient to support the animal's weight.

Douglas McCreery discussed the potential of intraspinal microstimulation for bladder control after SCI. Present sacral root stimulators elicit competing contractions of the bladder and external urethral sphincter. As the sphincter relaxes more quickly, micturition can be achieved in spurts, but dorsal rhizotomies are usually required. Intraspinal microstimulation may avoid these problems by activating the bladder without the sphincter. Sites that actively inhibit sphincter motoneurons may also exist.

The symposium concluded with a workshop chaired by Gerald Loeb. In his review Loeb identifies key problems in rehabilitation. He argues that despite their complexity, proven spinal cord mechanisms such as reciprocal inhibition and half-cycle oscillators are preferable to the idea of 'movement primitives.' He likens the control of human limb movements to that in puppets, the groupings of strings being equivalent to synergies. Understanding the functional groupings of spinal networks and their biomechanical actions is key to optimising rehabilitation strategies.

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