PERSPECTIVE

Reorganization of spinal neural circuitry and functional recovery after spinal cord injury

The ability of the adult central nervous system to reorganize its circuits over time is the key to understand the functional improvement in subjects with spinal cord injury (SCI). Adaptive changes within spared neuronal circuits may occur at cortical, brainstem, or spinal cord level, both above and below a spinal lesion (Bareyre et al., 2004). At each level the reorganization is a very dynamic process, and its degree is highly variable, depending on several factors, including the age of the subject when SCI has occurred and the rehabilitative therapy.

The use of electrophysiological techniques to assess these functional changes in neural networks is of great interest, because invasive methodologies as employed in preclinical models can obviously not be used in clinical studies.

Spinal neuronal circuits can be analyzed by recordings of the spinal reflexes (SR), which are evoked by non-noxious stimulation of cutaneous afferents of the tibial nerve and result, among healthy subjects, in an early SR component (60–120 ms latency) in the ipsilateral tibial anterior muscle. This reflex is thought to be involved in locomotion generating neuronal circuits in rats (Lavrov et al., 2006) and humans (Dietz et al., 2009). After an SCI, alterations in SR behavior occur (Dietz et al., 2009), in particular the early SR component decreases in amplitude at 6 months post-SCI, while a late component (120–450 ms latency) emerges. The late SR component becomes dominant and replaces the early one after about 1 year post-lesion. These changes are associated with a rapid exhaustion of leg muscle activity during assisted locomotion (Dietz, 2010). This abnormal behavior of SR in subjects with chronic incomplete SCI is correlated to their walking capacity, and suggests impairment of the spinal neuronal circuits underlying locomotion generation (Hubli et al., 2011). The shift from dominant early to late SR, due to the impaired supraspinal influence on spinal neural activity in subjects with motor complete SCI, could be reversed by activating spinal circuits with appropriate peripheral feedback during assisted locomotion on a treadmill.

While electromyography and nerve conduction techniques can assess almost exclusively the local spinal neuronal circuitries, of particular interest are also the investigation of the trigemino-cervical reflex (TCR) and trigemino-spinal reflex (TSR) responses, as well as of the (ILR) activity after SCI.

The TCR and TSR have been recently examined (Nardone et al., 2014) in a group of patients after traumatic incomplete (ASIA score B, C or D) SCI at cervical level. In healthy subjects reflex responses were registered from the sternocleidomastoid and splenium muscles, while no responses were obtained from upper limb muscles. Conversely, smaller but clear short latency EMG potentials were recorded from deltoid and biceps muscles in about half of the SCI patients. Moreover, the amplitudes of the EMG responses in the neck muscles were significantly higher in the SCI patients. These findings are thought to be the functional correlate of a reorganizational process that involves the pathways between trigeminal afferents and cervical spinal cord motoneurons. This reflex activity is likely to represent an expression of regenerative sprouting of fibers denied their original target populations by the SCI. The anatomical sites at which the trigemino-spinal reflex responses are integrated and propagate up the brainstem and down the spinal cord can be hypothesized on the basis of experimental studies. Since the TCR and TSR appear at the same latencies and share the same cranio-caudal progression as the motor responses involved in the startle reflex, it can been hypothesized that the anatomical neuronal pathways mediating TCR, TSR and startle reflex could be, at least in part, the same. The anatomical substrate for the startle reflex is well established in both animals and humans. Interneurons located in the reticular formation and the reticulospinal pathways are known to play a crucial integrative role. In fact, the motor activation pattern is generated in the nucleus reticularis pontis caudalis, and is transmitted directly to anterior horn cells through the reticulospinal tract (Davis et al., 1982). It has been demonstrated in animal models of SCI that the phylogenetically older reticulospinal system might provide a substrate for the functional recovery after corticospinal lesions and thus contribute to restoring improved motor performance (Baker, 2011). Although clearly secondary to the corticospinal tract in healthy function, the reticulospinal system could assume considerable importance after corticospinal lesion and may be a target site for therapeutic interventions (Baker, 2011). Motoneurons receive monosynaptic and disynaptic reticulospinal inputs; in particular the motoneurons that innervate intrinsic hand muscles receive monosynaptic excitatory connections. Reticulospinal fibers enter the grey matter in the zona intermedia and along the anterolateral and anterior surfaces of the anterior horns; their number decreases caudal to the cervical enlargement, where their place is taken by propriospinal fibres. In rats with incomplete SCI transected corticospinal tract axons which originally projected to the hind-limbs sprout and sent collaterals into the cervical grey matter where they contact with propriospinal neurons and increase their terminal arborization onto second motoneurons (Bareyre et al., 2004). In particular the C_{3-4} propriospinal interneuron system is thought to play a potentially important role in functional recovery after corticospinal lesion. Indeed, a great proportion of the descending drive to motoneurons came from reticulospinal pathways *via* propriospinal neurons. It has been recently demonstrated that severed reticulospinal fibers spontaneously arborize and form contacts onto a plastic propriospinal relay, thereby bypassing the lesion (Filli et al., 2014).

The establishment of new or previously silent synaptic connections may thus lead to an enhanced activity in the pathways mediating the trigemino-cervical-spinal reflexes, with recruitment of proximal muscles of upper limbs. However, it should be considered that assessing the spinal reflex activity might primarily reflect the functional state of the CNS, rather than rearrangements of specific supra- or intraspinal connec-

tions. The generation of new reflexes may thus be not specifically based on plastic brainstem-derived descending connections, but rather on a globally increased spinal excitability. Changes in descending innervation of spinal neural activity with consequent up- or down-regulation of several receptors have been implicated in symptoms of paralysis, spasticity, sensory disturbances and pain following SCI. Among the different neurotransmitters that may be involved in these processes, the monoamines are known to be important key regulators of motoneuron and spinal neural circuit excitability in the spinal cord. Interestingly, spinal adaptation was found to be accompanied by modifications at higher levels of control including the gigantocellular reticular nuclei from the mesencephalic locomotor region (Zörner et al., 2014). Anyway, the study of the trigemino-cervical-spinal reflexes can be used to demonstrate and quantify plastic changes at the brainstem and cervical level in patients following SCI. Further studies in a large cohort of subjects with a more homogenous degree of motor impairment could provide further insights into these reorganizational changes, assess their relation with clinical changes, and determine whether the observed abnormalities in trigemino-cervical-spinal reflexes may serve as objective outcome measure in the design of clinical trials.

The so called ILR, that is the involuntary contractions of hand and forearm muscles following stimuli delivered to lower limbs, interconnect lower and upper limbs and are also mediated by long propriospinal fibers. The enhancement of cutaneous and stretch-induced reflexes may lead to recruitment of distal muscles. The ILR are thought to reflect the consequences of synaptic connections formed between ascending afferent fibers and partially denervated cervical motoneurons. The prolonged delay between time of injury and emergency of intermimb reflexes suggest either regenerative sprouting and the development of new synaptic connections, or a strengthening of existing circuits in the spinal cord following SCI (Calancie et al., 2002). Interestingly, the strengthening synaptic contacts between afferent and efferent components do not appear to be providing any functional benefit to the subject, because these may limit the regenerative efforts of supraspinal pathways (Calancie et al., 2005). In fact, excessive or aberrant reorganisation in the central nervous system may also have pathological consequences, and the plastic reorganization can also be maladaptive.

In order to optimize functional recovery while minimizing maladaptive plasticity after SCI, it would be of great interest to clarify when and why spinal cord reorganization can be either "good" or "bad" in terms of its clinical consequences. The promotion of meaningful plasticity and of axonal regeneration are both necessary to advance the functional restoration.

In conclusion, a better understanding about the capability of the SCN to reorganize its circuits after injury is a key for developing rehabilitative strategies in persons with SCI. Electrophysiological studies may shed light on the functional mechanisms promoting the rewiring of lesioned motor tracts following SCI.

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