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Spinal cord injuries, human neuropathology and neurophysiology

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A correlative approach to human spinal cord injuries (SCI) through the combination of neuropathology and neurophysiology provides a much better understanding of the condition than with either alone. Among the benefits so derived is the wide range of interventions applicable to the restorative neurology (RN) of SCI so that the neurological status of the SCI patient is thereby much improved. The neurophysiological and neuropathological elements underlying these advances are described.

Key words: spinal cord injuries, restorative neurology, discomplete SCI

Introduction

Human spinal cord injuries (SCI) pose a massive human, public health and economic burden world-wide. In the USA alone it is estimated that over 250,000 persons are affected by SCI with the economic cost being in the order of a trillion dollars [1]. The enormity of the problem brings great pressure upon neuroscientists researching to find a cure for SCI despite the great difficulty imposed by the task. The major limiting factor in this respect is the inability of central axons to regenerate[2]. The setback due to lack of regenerative ability is further aggravated by Wallerian degeneration. In Wallerian degeneration the distal portion of the axon disintegrates progressively from the point of injury, caudally in the case of the descending efferent motor tracts and cranially for the afferent sensory pathways. Because of Wallerian degeneration experiments designed to rejoin the severed axons are totally flawed from the outset.

Therefore, an alternative approach to the problem posed by SCI is called for and this lies in the exploitation of limited but preserved neurological functions which may have escaped injury. In this regard it is a remarkable fact that in most SCI whether clinically complete or incomplete a small amount of residual white matter remains intact traversing the level of injury. This finding rests on both neurophysiological and neuropathological evidences and is the essence of this review. For instance, in a high proportion of otherwise clinically complete SCI patients conduction across the level of injury can be shown neurophysiologically. The term *discomplete* SCI has been introduced to describe this phenomenon. Various innovations have been introduced which enhance the function of these residual nerve fibers and as such improving the neurological status of the SCI patient. These methods form the armamentarium of the new discipline of restorative neurology (RN).

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Neuropathology of spinal cord injuries

In a series of 220 SCI postmortems it is found that there is no standard lesion, each case of human SCI is distinct so that they are never exactly similar. Everyone is an individual. This means that when an effective treatment is discovered it will need to be customized to suit each affected person individually in which case the standardized lesions produced in experimental animals would not be generally applicable.

In diving or motor vehicle injuries the spinal column is hyper-flexed or hyperextended causing disruption of ligatures and bony fractures of the vertebral column. As a consequence, the spinal cord is contused, crushed and lacerated. Total transection of the spinal cord is a rare finding. More often there is some continuity across the site of injury. Extradural or subdural hematoma formation is not a feature of human SCI. Clinically SCI is classified as being "complete" when there is total loss of sensation and voluntary motor control below the level of injury. The SCI is clinically "incomplete" when some degree of sensation and/or retained but limited voluntary movement is present. There is a third clinical category of SCI for which the term "discomplete" has been introduced[3]. In discomplete SCI there is absence of all sensation and voluntary movement below the level of spinal cord injury but in whom transmission of signals across the lesion can be shown neurophysiologically. This partial retention of neurophysiological function is supported by post-mortem findings in SCI patients which show that there is most often a small quantity of white matter i.e. axonal sparing at the level of injury in which case the term "anatomically" discomplete SCI is applicable [4,5].

Briefly the pathological changes found at post-mortem consist of compression laceration and central hemorrhagic necrosis of the spinal cord with a variable amount of preserved white matter at the periphery. A few hours after injury polymorphs infiltrate the lesion followed by lymphocytes and after a few days by macrophages which engulf the necrotic debris. A small amount of traumatic demyelination can be found at the early stage, limited to the level of injury. Softening (myelomalacia) of the spinal cord is also in evidence within 24 hours. Macrophage activity leads to multilocular cavity formation with astrocytes forming its wall and glial trabeculae crisscrossing the cyst. Within the walls of the cavity a small number of myelinated axons may be found. Following the injury, the myelinated pathways efferent and afferent undergo Wallerian degeneration. The myelin sheath breaks up into globules and the axons degenerate progressively both proximally and distally [6].

Neurophysiology of spinal cord injuries

In the normal human spinal cord learned tasks are associated with changes in the microanatomy of the cord as new networks are established. Motor control of muscle activity and movement is modified by the learning process in which the propriospinal network participates in addition to the recognized corticospinal voluntary motor pathway [7]. Surface poly-electromyography (PEMG) allows one to distinguish total spinal cord disruption from partial damage even in cases in which the syndrome is clinically complete. Standardized PEMG recordings of motor tasks enable patterns between injured and non-injured subjects to be compared [8,9]. PEMG also provides insights on how complex spinal systems combine to produce functional outcomes [10]. Two human SCI models are recognized by PEMG. Firstly, the less common type of injury in which the spinal cord is clinically completely anatomically disconnected from the brain. Secondly there are SCI patients in whom there is a partial spinal cord injury so that the segments below the level of injury receive a reduced and altered cortical input [3].

In SCI cases where the spinal cord is completely separated anatomically and physiologically from the brain the cord generates its own ipsilateral unsustained phasic proprio- and exteroceptive reflexes. In incomplete and discomplete SCI where there is partially retained residual brain influences, tonic segmental reflexes are observed even in the absence of any volitional muscle control [11,12].

With increasing suprasegmental conduction there is better motor control ranging between large and poorly organized flexion and extension movements to highly organized volitional postural and gait activity in which there is complete integration of segmental and suprasegmental functions [13].

Recovery from spinal cord injury depends on the presence of conducting axons and the locations of their endings within the spinal central grey matter [13]. Long loop reflexes between the brain and the spinal cord are dependent upon the integrity of both systems, upper and lower motor neurons. Complete or partial separation from the brain results in motor activity arising from local structures and synapses. Functional hierarchy of the spinal cord anatomically integrated with the brain results in functions which are dependent or independent of brain influences as may be demonstrated physiologically. The differences between anatomically integrated or anatomically dissociated motor activities of the spinal cord may be clearly recognized by physiological assessments [14]. There are several pathways which descend upon the anterior horn cells and the interneurons of the central grey matter of the spinal cord. The best known is the cortico-

spinal tract for voluntary movement. There are also the corticobulbar, or extrapyramidal, tracts and the peripheral nerve primary, secondary and tertiary afferents connecting with the spinal interneuronal network which possess widespread connections over many spinal cord segments. These interneurons integrate the numerous functions involved in producing harmonious movements [14].

The discomplete spinal cord injury syndrome

The term 'discomplete' SCI is applied to ASIA-A clinically complete cases of SCI in whom cortical influences below the level of the lesion can be identified by surface PEMG[3]. In discomplete SCI although there is absence of voluntary motor control below the level of the lesion neurophysiological evidence of residual conscious volitionally induced influence on spinal reflex activity below the level of injury can be found. Motor control and the pattern of motor unit activity recorded by surface electrodes in discomplete SCI is elicited through stretch reflexes, tendon vibration, attempted volitional activation of clinically paralyzed muscle groups, voluntary suppression of plantar withdrawal reflexes below the lesion and by reinforcement techniques such as the Jendrassic maneuver above the SCI lesion.

Concerning the frequency of the discomplete syndrome, in our experience of 88 clinically complete SCI cases examined electromyographically by PEMG, 74 (84%) were found to be discomplete and thus were the majority [15]. On the other hand "absolutely" complete SCI in which there is total absence of voluntary movement or sensation below the level of the lesion and in whom there is no neurophysiological evidence of supraspinal influence on the spinal reflexes below the lesion are in the minority.

There is currently an increasing number of reports of 'motor' discomplete[16] and 'sensory' discomplete cases appearing in the literature [17]. Nevertheless, there are still many attending SCI clinicians who believe that most clinically complete SCI cases are also in 'absolutely' complete group. These physicians seem to be incognizant of the existence of the discomplete syndrome which represents the majority of clinically complete cases. This lack of appreciation may be due to their belief that prominent spasticity arises only when there is 'spinal cord transection' arising from a segmental generator of hyperactivity below the level of the lesion. This misunderstanding needs to be corrected as follows. The interneuronal network presents a structurally dynamic entity which integrates many functions to produce harmonious voluntary movement and is a unified entity rather than being separated into two groups one spinal and the other supraspinal [18]. There exists a premotor neuronal pool which receives signals from above and from peripheral afferents [19]. Lesions of the descending voluntary and extrapyramidal pathways release the interneurons from brain control which then becomes an independent "generator of spasticity". Thus, released from cortical inputs, the interneurons sprout and network with peripheral afferents, creating new connections and so develops into a "new anatomy" generating spasticity [20].

Anatomical aspects

The neurophysiological evidence of transmission of signals across the level of injury in discomplete cases of SCI is supported by anatomical data as follows. In a post mortem study of 220 SCI cases 53 were found to be anatomically discomplete i.e. during life they had no voluntary motor control or sensation below the level of injury but who had anatomically a variable number of preserved axons traversing the lesion. This residual white matter was quantified in 3 of these discomplete cases being 1.12, 3.89, and 1.09 square mm. respectively. It is this residual white matter consisting of myelinated axons which conducts the neurophysiological signals observed to cross the lesion in discomplete cases of SCI [5]. In the incomplete and discomplete SCI patients the preserved white matter is responsible for the newly established profile of the residual brain descending system connections and their integration with the spinal network. Moreover, in studies of motor control in chronic SCI patients with multichannel surface PEMG it was shown that brain motor control diminished by SCI results in the establishment of a new distinct pattern of residual brain motor control. This is also the case for the quality of gait performance, which depends upon the extent of residual suprasegmental brain influence and brain control [21].

Restorative neurology

Restorative neurology is the branch of neurological science which applies active procedures to improve functions of the impaired nervous system through selective structural and functional modification of altered neurocontrol. It was first defined in 1982 at a Symposium on the Upper Motor Neuron. In restorative neurology under-unrecognized or altered neural functions are modulated by techniques which act on afferents and surviving neural circuits thus improving neurological status of the patient [22,23].

The human CNS has the ability to conduct neural impulses as spikes carrying information from inside and outside the body to, from and between hierarchically placed nuclei of the brain and spinal cord which then process this information to produce appropriate sensory perception

and motor output. The conducting pathways are made up of multi-parallel axons of different diameters, conduction velocities and lengths reaching neural processors that are of different sizes and shapes, located within the gray matter and constructed from populations of interneurons with short axons. These two basic functional features of the CNS, to conduct and to process, provide sensory perception, cognition, and a wide variety of movements, from locomotion to learned skills and speech.

The systematic use of a comprehensive protocol for multichannel surface PEMG recording, which was developed as a method for brain motor control assessment (BMCA) is a very useful protocol in assessing SCI neurophysiology. BMCA is able to quantitatively describe the characteristics of motor control recovery in persons with SCI. Key information is contained in the overall spatiotemporal pattern of motor unit activity, observed in the PEMG envelope. In incomplete SCI patients, in addition to the methods that are applied in patients with complete motor lesion (proprioceptive and exteroceptive reflexes, motor unit and microneurographic studies, etc.) neurophysiological studies during volitional motor activity should also be included. Three functions of the upper motor neuron are studied in this context:

A. preservation or deterioration of volitional activity;
B. the effects of remote muscle contraction on paretic, or paralyzed muscles;
C. features of stretch and withdrawal reflexes.

In Restorative neurology, rather than focusing on the deficits and lost function caused by upper motor neuron lesions or disorders it is more advantageous to elucidate, in each individual, the specific neural functions that remain intact and from there, to build upon the preserved functions by designing a treatment protocols to optimize their effectiveness and thus improve recovery.

Theoretically there are two means by which neural processing and restoration of upper motor neuron functions may be modified, firstly anatomically, through reconstructive neurosurgery and secondly by fostering functional restoration through restorative neurology. Both approaches are applied in the modern practice of restorative neurology such as by physical therapy and applied neurophysiology as well as by pharmacological, functional neurosurgical and neurobiological means. Reconstructive neurosurgery consists of tendon or peripheral nerve transplantations. Neurobiological methods explore the potential for neurotrophins and stem cells to differentiate into becoming nerve cells, which may then theoretically be able to search for and recognize appropriate target neural circuits and thus to restore function – but to the present such results remain to be demonstrated.

In our experience SCI neural damage is almost never total as determined neurophysiologically or morphologically by autopsy (see above). In human SCI there are almost always some surviving and functioning neural tissues that, depending on their newly establish relationships; will generate clinical and sub-clinical residual movements. Neurophysiological methods designed for the assessment of processing and conducting neural systems are capable of elucidating and measuring the characteristics of such residual functions.

The spinal cord, being the output organ of the central motor system, has a fundamental role in the restoration of motor function. The spinal cord consists of neural networks located within its central gray matter with long white matter intersegmental connections as the pro-propriospinal system. Descending efferent tracts are the corticospinal, reticulospinal, vestibulospinal, rubro and tectospinal pathways. This spinal neural circuitry integrates the nervous system as a common final network within which is executed the motor control required for reflex activities, volitional, postural and gait. Their descending influence is exerted over the control of reflexes at the interneuron level. These descending voluntary and extrapyramidal motor systems converge upon primary afferents connecting to the interneuron pool and from there projecting to the motor neuron. The capacity of the spinal cord to integrate converging signals is retained even in the absence of brain input as shown by sustained electrical stimulation of posterior nerve roots. Different strengths, site and frequency of posterior root stimulation can elicit functional and non-functional motor output patterns [24]. This finding is applied in the clinical practice of restorative neurology through the augmentation and modification of residual motor control [25].In the clinical practice of restorative neurology the modification of the spinal cord network configuration is accomplished by electrical stimulation of afferents of peripheral nerves, posterior roots and posterior columns which elicits a central state of the excitability. Such excitability is required to be maintained at an operational level to generate a functional motor output. It is also essential that this central state should be in dynamic equilibrium between excitatory and inhibitory mechanisms within the processing networks. In addition, pharmacological intervention to support and maintain this equilibrium can be of additional value [26].

Discussion

The spinal cord has a regular segmental structure with long white matter ascending and descending pathways placed peripherally and with the gray-matter neural networks centrally located. The human lumbar spinal cord is not simply a relay system between brain motor pathways and spinal motor neurons [27]. Its role within an integrated nervous system is that of a common processing

network for the execution of voluntary motor movement as well as for local reflexes, posture, and gait. The lumbar spinal cord gray matter contains a large population of interneurons which form neural circuits, the functional organization of which is flexible and subject to plasticity giving it a multifunctional character providing modulatory actions, reconfiguration, and flexible operation. In this way the lumbar spinal cord may be considered to be a "spinal brain" [26,28].

Electrical and magnetic spinal cord stimulation provides a reliable way in which to characterize neurophysiological and pathological aspects of spinal cord functions. Moreover, transcutaneous direct current stimulation and repetitive magnetic stimulation holds therapeutic promise for patients with spinal cord injuries. To the present the number of findings from epidural or transcutaneous spinal cord stimulation in paralyzed chronic spinal cord injury is limited to observational and neurophysiological studies in a relatively small numbers of subjects. Well-designed scientific studies are needed to consolidate our theoretical and practical knowledge of Human Motor Control and the neurophysiology of upper motor neuron dysfunction. Briefly we are beginning to learn how to perform external modifications of upper motor neuron function by external control of afferents to the spinal cord. External electrical stimulation of posterior root afferents has the potential to facilitate neuroplasticity. Neuroplasticity is defined as the ability of neurons and neuron networks to adjust their activity and their morphology from alterations in their environment or patterns of use [29]. External control of afferents facilitates the development of neuroplasticity in SCI [30].

Conclusions

Clinical research designed to improve the quality of spinal cord patients' recovery has given promising results. For instance, we have discovered that there are many diverse methods which can restore movement after injury in complete, discomplete and incomplete SCI as shown above. This beneficial outcome is best explained in two parts: firstly by gaining extensive knowledge and data from healthy spinal cord systems and secondly by a new approach of managing spinal cord injury as a structured, multi-modal program with on point analysis and measurements. A remarkable fact is that SCI has little or no finality and what we may see as damaged spinal cord neural systems actually are useful in ways which we continue to discover. It will be seen that well administered care of the spinal cord injury patient which incorporates all possible approaches and new discoveries leads to remarkable spinal cord injury recovery rates.

Author contributions

MRD: neurophysiology; BAK: neuropathology

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