Artificial Organs

Review

Neurocontrol of Movement in Humans With Spinal Cord Injury

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Abstract: In this review of neurocontrol of movement after spinal cord injury, we discuss neurophysiological evidences of conducting and processing mechanisms of the spinal cord. We illustrate that external afferent inputs to the spinal cord below the level of the lesion can modify, initiate, and maintain execution of movement in absence or partial presence of brain motor control after chronic spinal cord injury. We review significant differences between spinal reflex activity elicited by single and repetitive stimulation. The spinal cord can respond with sensitization, habituation, and dis-habituation to regular repetitive stimulation. Therefore, repetitive spinal cord reflex activity can contribute to the functional configuration of the spinal network. Moreover, testing spinal reflex activity in individuals with motor complete spinal cord injury provided evidences for subclinical residual brain influence, suggesting the existence of axons traversing the injury site and influencing the activities below the level of lesion. Thus, there are two motor control models of chronic spinal cord injury in humans: "discomplete" and "reduced and altered volitional motor control." We outline accomplishments in modification and initiation of altered neurocontrol in chronic spinal cord injury people with epidural and functional electrical stimulation. By nonpatterned electrical stimulation of lumbar posterior roots, it is possible to evoke bilateral extension as well as rhythmic motor outputs. Epidural stimulation during treadmill stepping shows increased and/or modified motor activity. Finally, volitional efforts can alter epidurally induced rhythmic activities in incomplete spinal cord injury. Overall, we highlight that upper motor neuron paralysis does not entail complete absence of connectivity between cortex, brain stem, and spinal motor cells, but there can be altered anatomy and corresponding neurophysiological characteristics. With specific input to the spinal cord below the level of the lesion, the clinical status of upper motor neuron paralysis without structural modification can be modified, and movements can be initiated. Thus, external afferent input can partially replace brain control. **Key Words:** Neurocontrol—Spinal cord injury—Afferent inputs—Motor control—Functional electrical stimulation.

Movements—skillful, repetitive, single or multijoint, coordinated, reflex, automatic, postural—have been studied by kinematic and kinesiological, biomechanical, functional anatomical methods. With the development of neurophysiological methodologies, it became possible to study how the nervous system controls movement: neurocontrol of movement. In the past several decades, development of noninvasive methods for stimulation, external control, and recording of peripheral and central functions of the human nervous system advanced our knowledge of neurocontrol of movement and its organization.

The spinal cord as part of the central nervous system is present in all vertebrates and for nearly two centuries has been extensively studied for its anatomical, physiological, and biological characteristics (1). Its understanding underwent several conceptual phases. Bell in the early 19th century described the spinal cord as "the way in and the way out" to and from the brain (2). Thus, it was seen for its conducting properties. Sherrington added the concepts of reflex activity and their integration (3). Years later,

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Lundberg brought to the conceptual understanding of spinal cord function the principle of the premotor center (i.e., last-order interneurons converging peripheral and central inputs) (4). Finally, through Grillner's work, the ability of the spinal cord to intrinsically generate repetitive, rhythmic movements was recognized (5).

Here, we shall review our work and discuss the status of neurophysiology of the human lumbar cord involved in motor control when completely or partially deprived of brain control from the brain, brain stem, and cerebellum and discuss the processing capabilities of the human lumbar cord. In addition, we shall address the significance of the spinal cord network for the interpretation of complex descending input in order to generate functional movement, initiated and controlled by the brain. We shall discuss how sustained stimulation of lumbar posterior roots below the level of the lesion can induce and/or augment spinal cord motor output in absence of brain motor control. We shall compare neurocontrol elicited by epidural stimulation of posterior structures of lumbar spinal cord deprived of and with partially present brain motor control.

Early investigation of repetitive reflex activity

Through the past two centuries, human spinal cord motor control has been studied by a variety of reflex activities, and motor outputs to volitional motor tasks. Advancements were made by the introduction of surface and needle electromyography (EMG) and evoked neurograms, which allowed measurements of time, location, and size of motor responses. In our early studies, we have examined in the population of individuals with chronic spinal cord injury features of spasticity, tendon jerks, and cutaneo-muscular reflexes using surface EMG (6–11).

Before, reflexes and their modification were mostly studied by applying single stimuli or conditioning test paradigms. The emphasis in human reflex studies has been on reflex pathways, their latencies, and their reciprocal relation. We examined repetitive stimulation in spinal cord injury subjects and showed regularly elicited tendon jerks can result in progressive decrease in size after hundreds of stimuli (Fig. 1A) (11). This decrease in size was not evident when the interstimulus intervals or stimulation amplitudes were of stochastic nature (11). Thus, repetitive elicited monosynaptic reflex responses in humans lacking brain motor control revealed the feature of habituation: a progressive decrease of size of reflex responses, to constant and regular reflex stimulation.

Another reflex activity of significant value for studies of the spinal cord is the cutaneomuscular withdrawal reflex. Regular repetition of its elicitation by electric stimulation revealed a characteristic pattern of behavioral modifications of its amplitudes. With constant stimulation strength and frequency, there is an early, relatively fast sensitization followed by a slow habituation of the response amplitudes (Fig. 1B) (9). Furthermore, the speed of this sensitization and habituation depended on the stimulation frequency. Higher frequencies led to faster sensitization as well as faster habituation (10).

Moreover, in chronic spinal cord injury subjects with severe spasticity, or in other words with increased central state of excitability of the spinal cord below the injury, it is possible to demonstrate patterned responses of thigh and leg muscles after a single tendon jerk (Fig. 1C) (7). These afterdischarges follow the monosynaptic component of the tendon jerk as a sustained, prolonged tonic activity or repetitive phasic activity. Furthermore, this can happen simultaneously in ipsilateral agonist and antagonist muscle groups, as well as in the muscles of the contralateral leg. Instead of responses in the muscle corresponding to the tapped tendon, there is the possibility of additional polysynaptic, long-lasting responses in practically all muscle groups below the level of the lesion. In summary, repetition of reflex elicitation revealed behavioral modulation of reflex amplitude and size. Mechanisms of habituation, dis-habituation, sensitization, and generation of motor responses through their interaction were found. It is of interest that these central mechanisms can be also present in the modulation of the monosynaptic components of repetitively elicited tendon jerks (11).

Previous studies of human spinal cord injury have shown that residual influence on segmental reflex activity can be present in motor complete spinal cord injury. For this condition, we proposed the term "discomplete" to indicate the presence of brain, supraspinal influence below the level of injury on spinal reflex activity. This means that absence of volitional motor activity does not preclude the existence of axons traversing the injury site and influencing the activities below the level of the lesion (12,13). The majority of individuals with complete lesions will, in time, regain at least some of their nervous system functions, even in the absence of clinical evidences of such. In addition to "discomplete," there is human model of "reduced and altered motor control." Unlike "discomplete," this is a spinal cord injury model of retained residual brain motor control (14).

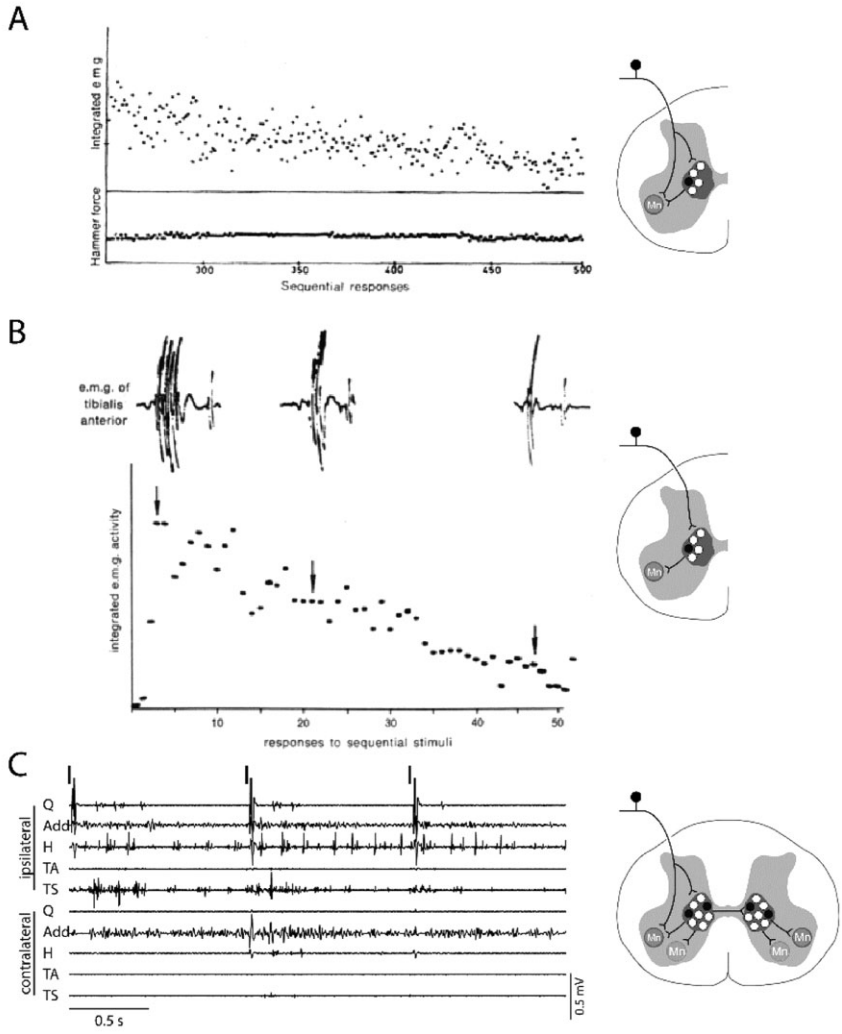

FIG. 1. (A) Histogram of integrated EMG activity due to repeated taps on the Achilles tendon, applied regularly with a hammer (reproduced from Dimitrijević and Nathan [11]). With repetitions, the response size successively decreases, habituates. (B) Histogram of integrated EMG activity in response to sequential plantar stimulation in tibialis anterior. Arrows show EMG samples (reproduced from Dimitrijević and Nathan [9]). Initially, there is a steep rise or sensitization of response size followed by a relatively slow habituation. (C) Responses to patella jerks in chronic spinal cord–injured individual with spasticity. Monosynaptic responses in quadriceps were followed by an afterdischarge. Various tonic and clonic afterdischarges were also present in multiple ipsi and contralateral muscle groups. On the right side, sketches of the tentatively involved pathways are illustrated. Q, quadriceps; Add, adductor; H, hamstrings; TA, tibialis anterior; TS, triceps surae.

Epidural stimulation and functional electrical stimulation

In parallel with neurophysiological studies of motor control in humans with spinal cord injury, work on functional electrical stimulation (FES) was initiated and introduced in research and clinical practice of the external control of paralyzed movements due to upper motor neuron dysfunctions (15–17).

Clinical studies of FES in subjects with upper motor neuron dysfunction revealed that in addition to the stimulation of motor fibers of peripheral nerves for correction of "central paresis," there is also an effect of stimulation of large afferent axons of the peripheral nerves. Site of stimulation and setup for motor or sensory axons introduced FES as a tool for modifying of central processing capabilities of the central nervous system.

In 1973 and the subsequent years, Cook and Weinstein (18), Dooley and Sharkey (19), and Illis et al. (20) reported independently on the effectiveness of spinal cord stimulation for modification of motor control in patients with upper motor neuron disorders (21).

At that time, everything was ready to integrate developed noninvasive methods for the assessment of human spinal cord motor functions together with external electrical input through afferents as an intervention for modification of upper motor neuron functions. Furthermore, supportive experimental animal work has been undertaken for this significant step to restore impaired functions by electrical stimulation of the mesencephalic locomotor region (22,23). The propriospinal and reticulospinal systems for initiation of stepping were also recognized (24).

Existing methodologies for epidural stimulation in multiple sclerosis patients with spastic paralysis (18–20,25) and the demonstration of the effectiveness of spinal cord stimulation to induced locomotion in adult cats (26) led us to explore sustained, nonpatterned electrical stimulation of posterior

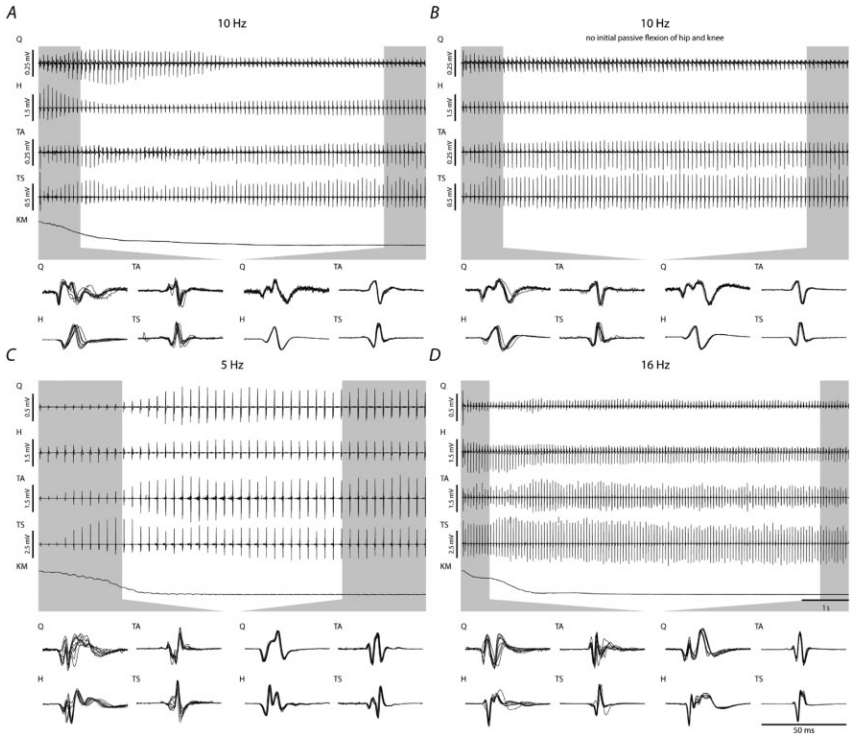

FIG. 2. Lower limb extension in response to epidural stimulation of the lumbar posterior roots in an individual with motor complete spinal cord injury. Effect of epidural stimulation on a leg that is initially in passive hip/knee flexion (A) in comparison to no passive hip/knee flexion with the same stimulation conditions (B), i.e., 10 Hz, 3-0 + , 10 V. A clear extension movement was evident in A with concomitant characteristic modulation of the elicited compound muscle action potentials (CMAPs). This effect of CMAP modulation was not evident if the leg was not initially passively flexed (B). C and D show examples with initially, passively flexed hip/knee at 5 Hz (C) and 16 Hz (D; C: 5 Hz, 0-3 + , 5 V; D: 16 Hz, 0-3 + , 5 V). Note that besides the modulation of the reflex amplitudes, also the CMAP shapes were modulated during the extension movement (A, C, D). Every subfigure shows 8-s long traces from the onset of the stimulation in four muscle groups and the corresponding knee movement if the knee was initially, passively flexed. Below, the traces are the initial and the last 10 CMAPs of all four muscle groups illustrated as a superposition of the CMAPs normalized to the peak-to-peak amplitude. All recordings were performed in the same subject on the same day. Q, quadriceps; H: hamstring; TA, tibialis anterior; TS, triceps surae; KM, knee movement.

lumbar structures on initiation of locomotion in subjects with chronic clinically motor complete spinal cord injuries (27). We documented that spinal cord stimulation of the upper segments of lumbosacral cord can elicit locomotor-like EMG activity and stepping movement. We induced rhythmic locomotor activity by placing a quadripolar stimulating electrode in the epidural space and applying an electrical train of stimuli of 25–50 Hz, with stimulus strength from 5–9 V. This finding suggests that when the integrity of segmental input–output was preserved, the lumbosacral network's mechanisms determined the temporal pattern of rhythmic generation, and motor-output shaping was able to initiate and maintain locomotor-like activity in response to nonpatterned simulation of a particular site, depending on the specific strength and amplitude of frequency (27).

The dependence of the motor output from the rate of afferent stimulation, the fact that reflexes can be behaviorally modulated, and various technological advancements led to the studies of spinal cord reflexes and their behavior after application of different profiles of sustained, nonpatterned stimulation of the posterior roots from the epidural space. These reflexes were termed posterior root–muscle reflexes after their initiation and recording sites (28). Before that, it was only possible to stimulate at low-frequency (1–2 Hz) the afferent fibers of single peripheral nerves. Epidural stimulation extended the methodological possibilities to simultaneous stimulation of virtually all lumbar posterior roots at low and high frequencies (up to 130 Hz).

By applying epidural posterior root stimulation, two functional movements of the otherwise paralyzed legs of humans with motor complete spinal cord injury could be elicited: extension (Fig. 2) (29) and rhythmic activity (Fig. 3) (27,28,30).

Lower limb extension

Jilge et al. (29) investigated lower limb extension in five individuals with motor complete spinal cord injury. This work is reviewed in detail in the following paragraphs. All subjects were healthy adults with

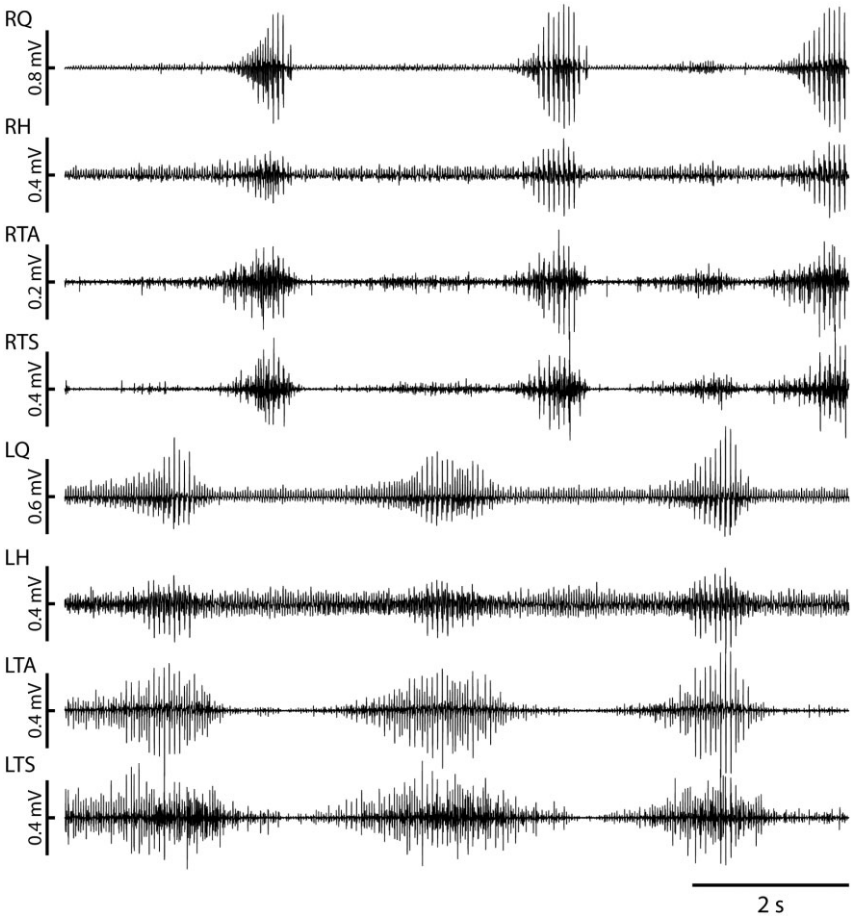

FIG. 3. Rhythmic activity in response to epidural stimulation in an individual with motor complete spinal cord injury. In the illustrated case, all muscle groups of the same leg are coactive at the same time, but activity is reciprocal between the limbs (stimulation parameters: 31 Hz, 10 V). All activities consist of stimulus time-locked compound muscle action potentials whose amplitudes were modulated to form the rhythmic patterns. Q, quadriceps; H, hamstring; TA, tibialis anterior; TS, triceps surae; L, left; R, right.

closed post-traumatic spinal cord lesions, with a chronic lesion (>1 years post injury), no current use of antispastic medication, preserved stretch and cutaneomuscular reflexes, and no voluntary activation of motor units below the level of the lesion, as confirmed by brain motor control assessment (31) and present lumbosacral-evoked potentials (32). There was no sensory function below the level of the lesion in four of the subjects studied, while one subject showed tactile impairment and unaltered cortical somatosensory-evoked potentials elicited by stimulation of the peroneal and tibial nerves. All subjects had an epidural electrode array implanted at a vertebral level ranging from T12 to L1.

A bilateral extension of the lower limbs could be initiated in subjects with complete SCI by applying nonpatterned lumbar posterior root stimulation (29). Continued stimulation could actively maintain the extended position. The amount of extensor muscle activity depended on the stimulation frequency, with the range of 5–15 Hz being most effective. The EMG recordings revealed larger posterior root–muscle reflex amplitudes in the extensor than in the flexor muscle groups. The results were well-defined modulations of the reflexes during the movement. Figure 2 illustrates these posterior root–muscle reflex modulations at different frequencies including with and without the initially passively flexed limb. Stimulation with frequencies at and above 20 Hz induced a short initial movement toward the extended position followed by a flexion that remained over the ongoing stimulation. Thus, lower limb extension is a response occurring only in a range of stimulation frequencies (below 20 Hz).

That led to the question of whether and how the ability to stand can be restored after spinal cord injuries. Pratt et al. (33) have studied the effect of standing training on the weight-bearing capacity in cats with chronic spinal cord injuries. Using the same design, De Leon et al. (34) investigated whether the observed recovery may have been spontaneous rather than an effect of the training. Their conclusion was that training was indeed causal to the observed results, indicating long-term changes. It was shown that step and standing training in chronic incomplete SCI subjects can restore the ability of short, weight-

bearing standing (35,36). Furthermore, in a single subject study, bilateral extension with enough force to be weight-bearing could be induced by epidural stimulation in a clinically motor complete spinal cord injury subject (37).

The summarized results illustrate that a sustained extension of the lower limbs can be obtained in supine position. This approach does not require any preparation to be carried out. The movement starts immediately after stimulation is turned on. This highlights that the ability to induce an extension of the lower limbs remains after chronic clinical motor complete spinal cord injury.

Demonstration that posterior spinal cord transcutaneous stimulation is also effective opens the possibility to evaluate motor and responses to transcutaneous stimulation before performing the invasive procedure of epidural stimulation (38,39), and therefore, it will be possible to expand clinical programs.

Rhythmic motor unit activity

Minassian et al. (28) studied rhythmic motor output in response to epidural spinal cord stimulation in humans with motor complete spinal cord injury. We shall outline this work here.

Epidural stimulation with frequencies in the range of 25–50 Hz induced burst-like EMG activity in the lower limb muscle groups leading occasionally even to stepping-like movements with reciprocal relation of the bursts between antagonist muscles. Increased stimulation frequencies (i.e., above 50 Hz and up to 100 Hz) led to decreased amounts of motor output and muscle tone. Rhythmic activities at 25–40 Hz consisted of separate CMAPs that were modulated (Fig. 3). At 40 Hz and above, the CMAPs tended to merge and EMG activity was no longer unequivocally identifiable as belonging to a single stimulation pulse. This sustained nonpatterned stimulation not only activated neural structures eliciting reflexes but also recruited mechanisms involved in the modulation of their pathways.

The authors (28) concluded that when epidural stimulation induced rhythmic EMG activities in the lower limbs, the output is due to afferent volleys entering the spinal cord via large diameter fibers within the posterior roots (40). These stimulated structures are believed to be a subset of the fibers that would be involved in sensory feedback while a person with an intact nervous system walks. During locomotion, receptors would generate phasic and tonic activities that would be transmitted by these structures to the lumbar spinal cord via the posterior roots. These input signals would be comparably complex in their temporal and spatial structure. Further complexity arises from brain-controlled, presynaptic gating of this input. Yet the epidural stimulation as it was applied in these studies (27–29) was of sustained, tonic nonpatterned nature, generating input with little information to all lumbar and upper sacral posterior nerve roots. Thus, this epidural input was very different to sensory feedback during locomotion. The authors (28) speculated "that the input acts also as a common drive to spinal interneuronal networks located in the lumbar cord" and that the nonpatterned peripheral input signal "is interpreted as a central command signal," organizing the lumbar spinal network by "temporarily combining them into functional units." Interestingly, the generation of rhythmic EMG activity or extension-like motor output varied with the stimulation frequency. In addition to stimulation frequency, other factors such as subclinical brain influences, central state of excitability, and interneuron characteristics are also important contributors for configuring the spinal cord network. Five to 15 Hz induced an extension, while >20 Hz did not do so but had a possibility to evoke rhythmic EMG activity. These effects of frequency were observed even when other stimulation parameters remained constant (29). The authors (28) suggest that the cause is related to the flexibility of operation of spinal interneuronal networks and their multifunctional character as well as the connectivity of the activated large-diameter sensory neurons with these networks. This agrees with the findings of Hultborn et al. (41) who have shown in cats that there are reflex pathways that directly synapse to the central pattern generator.

Thus, Minassian et al. (28) proposed that the studied model of the human lumbar cord isolated from brain control by accidental injury has features resembling a central pattern generator for locomotion as in mammals like cats, rats, rabbits, dogs, and nonhuman primates (cf. Dimitrijevic et al. [27]).

The ability of the lumbar spinal cord of individuals with complete spinal cord injury to respond rhythmically and tonically (as it is with the extension movement) depends partially on the input parameters, and mainly on the stimulation frequency (Fig. 4). Yet all epidurally generated inputs were nonpatterned in their nature.

The postulated effects of epidural stimulation on the spinal networks are illustrated in Fig. 5. From the results thus far, we can conclude that alteration of frequency of spinal cord stimulation within a narrow range and with constant strength can evoke two strikingly different functional movement modalities: tonic and rhythmical activity. We hypothesize that a

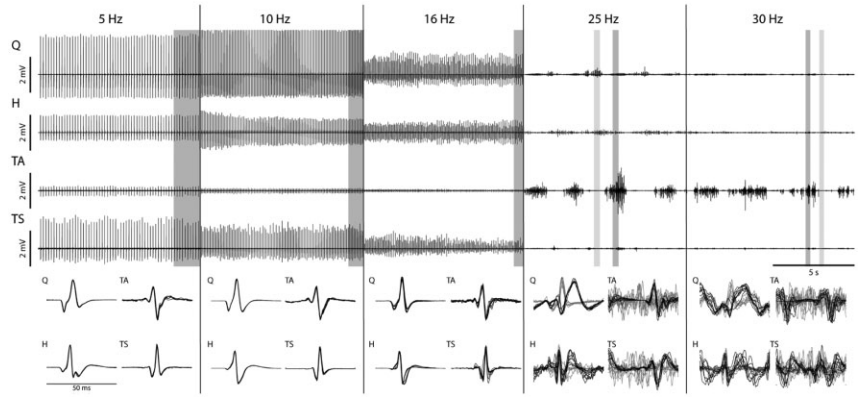

FIG. 4. Example of the effect of subsequently increased stimulation frequency with all other parameters (stimulation intensity, pulse width, electrode position) kept constant. A general trend of decreasing response amplitude with increasing stimulation rate is visible. This trend is reversed in tibialis anterior (TA) at 25 Hz when it starts to produce rhythmic activity. During the bursts, even the amplitude of the relatively unconditioned 5 Hz responses were surpassed. Concomitant to the modification of the reflex sizes, also their shapes and latencies were modified. Prolonged latency responses occurred in muscle groups active when TA is bursting during rhythmic reflex modulations. Top: 10-s traces of epidural spinal cord stimulation with 5, 10, 16, 25, and 30 Hz at the common threshold of posterior root–muscle reflex elicitation (6 V) are illustrated. Below are 10 compound muscle action potentials (CMAPs) of all four muscle groups illustrated as a superposition of the CMAPs normalized to the peak-to-peak amplitude. The CMAPs correspond to the shaded area of the traces above. For 25 and 30 Hz, CMAPs are extracted from both burst phases; the gray and the black superposition correspond to the light and dark gray areas of the above traces, respectively. Q, quadriceps; H, hamstring; TS, triceps surae.

sustained train of input is needed; the central state of responsiveness of the spinal network and other cellular and synaptic connectivity are factors contributing to configuration of the interneuronal network to respond with a functional output.

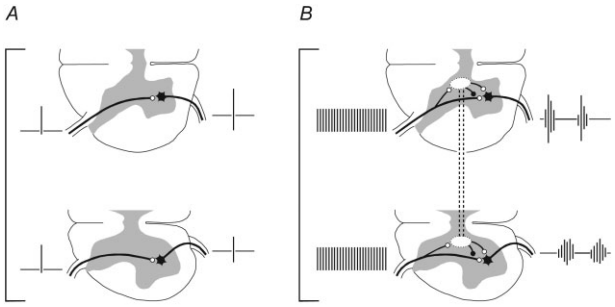

FIG. 5. Conceptual illustration of the effects of epidural posterior root stimulation. (A) The monosynaptic reflex pathway. Epidural stimulation induces discrete volleys of action potentials in the posterior roots that, in turn, activate the motoneurons over the Ia afferent to motoneuron synapse. Compound motor action potentials are recorded from the corresponding muscles. These reflexes are called posterior root–muscle reflexes. (B) Stimulation with a train of stimuli. Every stimulation pulse still produces a posterior root–muscle reflex through the Ia afferent to motoneuron synapses, but the reflexes are additionally modulated. The interneuronal network through afferent input of a certain rate is configured to rhythmically modulate the reflex activity by pre- and postsynaptic action onto the motoneurons. When a single stimuli is applied (A), interneurons are also activated, but their modulative action onto the motoneurons is not seen or is expressed as a polysynaptic response or afterdischarge. Continuous stimulation with a certain rate is thought to be necessary to put the network into a functional state, that is, rhythmic output (as in B), extension, or even additional functions.

The next section reviews the interaction of nonpatterned epidural stimulation with step-related feedback as generated by treadmill stepping.

Epidural stimulation and treadmill stepping

Ongoing basic research investigates spinal reflex circuits, the organization of inputs to spinal interneuronal populations, and the flexibility of operation of interneuronal circuits. The spinal lumbar network can integrate and interpret both the epidural stimulation and other peripheral and proprioceptive inputs in order to generate motor output. Minassian et al. (42) studied the interaction of inputs provided by epidural stimulation and manually assisted treadmill stepping in two sensory and motor complete individuals (example data are illustrated in Fig. 6).

During treadmill stepping alone, EMG patterns are characterized by low amplitude and co-activation in the stance phase and at the end of the swing phase. These patterns were elicited only by the step-related sensory feedback due to treadmill stepping (Fig. 6A). Quadriceps showed little, or no EMG activities. Thus, proprioceptive sensory feedback alone was not sufficient to generate a locomotion pattern in the two observed subjects.

By adding epidural stimulation to the treadmill stepping, multiple EMG patterns were recorded from the subjects. The nature of the patterns varied with the applied stimulation frequency. Frequencies below 20 Hz—as in the lying supine position—

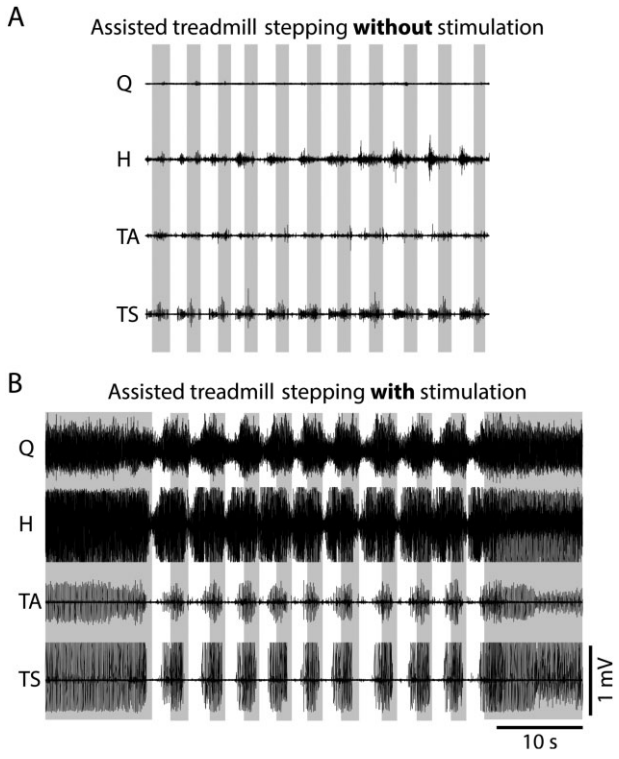

FIG. 6. Example of the combined effect of manually assisted treadmill stepping and epidural spinal cord stimulation in an individual with motor complete spinal cord injury. (A) Electromyographic (EMG) activity during manually assisted treadmill stepping at 1.3 km/h. (B) EMG activity during manually assisted treadmill stepping with concomitant epidural stimulation (30 Hz, 10 V). At the beginning and at the end of the recording, the subject is standing. Gray areas mark the stance phases. EMG activity is markedly increased with spinal cord stimulation. Tibialis anterior (TA) and triceps surea (TS) show a complete suppression of the activity between the bursts, even though the spinal cord stimulation-induced EMG activity during standing is comparable in size to the bursts. All EMG activities were comprised of stimulus time-locked compound muscle action potentials. Although, TA and TS were only responding to every fourth stimulus with a compound muscle action potential. Q, quadriceps; H, hamstrings.

produced tonic motor output constituents of stimulus time-related compound motor action potentials, posterior root–muscle reflexes that were rather constant during standing and modulated during passive stepping. With stimulation frequencies above 50 Hz, motor outputs could even be completely suppressed. Finally, stimulation frequencies around 30 Hz with concomitant step-related feedback induced burst-like rhythmic modulations of the posterior root–muscle reflexes (Fig. 6B). Thus, stimulation frequency was again instrumental in setting up the lumbar interneuronal networks to generate rhythmic motor activity. It is noteworthy that the different motor outputs were all produced under unchanged conditions of the peripheral feedback.

The influence of the stimulation strength corresponded to the amount rather than the quality of the responses. Increased stimulation intensity increased the response amplitudes of the rhythmic responses to appropriate stimulation frequencies (20–50 Hz). Stimulation intensities that were below motor threshold during standing could produce stimulus time-related compound motor action potentials when step-related feedback was added by manual assisted treadmill stepping. The result was burst-like activity synchronized to the stance and swing phases. At this low stimulation intensity, compound muscle action potentials were not present during these activities. Increased stimulation intensity revealed previously not present stimulus time-related compound motor action potentials that constituted the burst-like EMG activities. Furthermore, the timing of the rhythmic EMG activities was not necessarily functional (cf., example in Fig. 6). For instance, the quadriceps in two separate recordings were bursting during the swing phase as well as during the stance phase. It is also noteworthy that in the case of epidural stimulation in supine position and without peripheral input, various "nonfunctional" co-activity and reciprocity patterns between the muscle groups exist. In fact, the pattern where all muscles of one leg burst simultaneously (cf., Fig. 3) is most frequently observed (30,43).

We are speculating that the tonic components of inputs provided to locomotor circuitry by epidural stimulation are essential to activate its innate capability to generate rhythmic activities and to maintain its operation. The patterned step-related input triggers entrains its activity but would not by themselves be able to maintain a sustainable state of excitability to produce rhythmic activities.

Volitional influence onto epidurally induced rhythmicity in incomplete spinal cord injury

Finally, we are presenting here previously unpublished data on the effect of volitional influence on rhythmic motor outputs that were generated in response to epidural spinal cord stimulation subjects with incomplete spinal cord injury. For that purpose, four individuals with incomplete spinal cord injury (four individuals, three of whom were ambulatory) were studied during epidural stimulation with the same protocol as in Minassian et al. (28) in sitting position. When a stimulation configuration was reached where rhythmic modulation of posterior-root–muscle reflexes occurred, the subjects were asked to volitionally interfere and modify the motor output by performing the volitional motor task. An example is illustrated in Fig. 7. Epidural stimulation evoked rhythmic motor activities that were increased

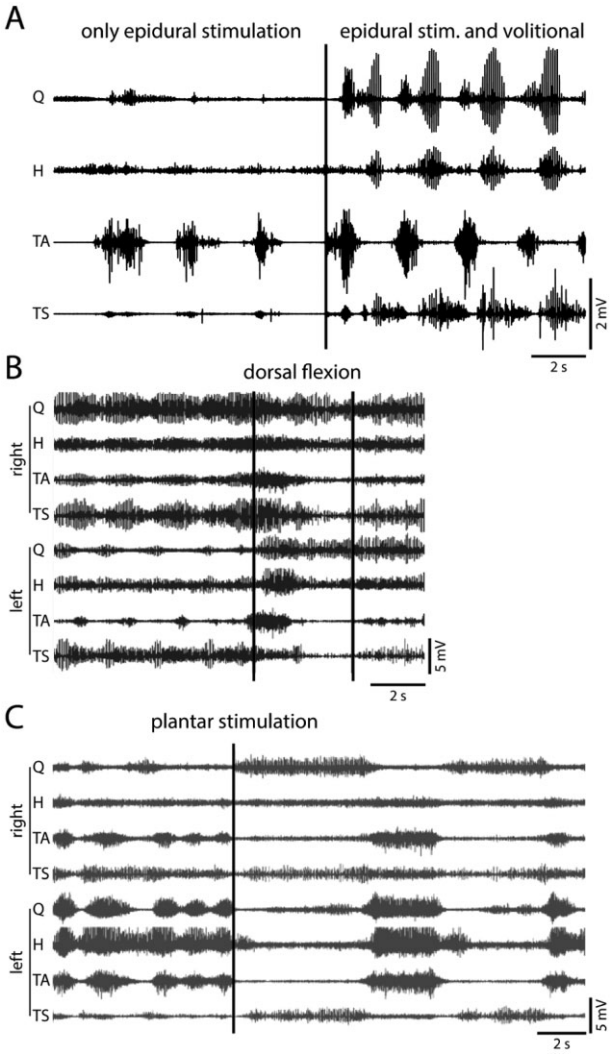

FIG. 7. Interaction of epidurally induced rhythmic motor activity with volitional action and plantar stimulation in an individual with incomplete spinal cord injury. (A) Modification of present rhythmic activity by volitional performance of cyclic dorsal plantar flexion. The left side illustrates the electromyographic (EMG) activity that was induced by 25 Hz of epidurals spinal cord stimulation (9 V). The line in the middle marks the time when the subject was asked to volitionally perform cyclic, alternating dorsal-plantar flexions. The amplitude of the outputs in all channels was markedly increased. Previously not present reciprocity between tibialis anterior (TA) and triceps surae (TS) was established and quadriceps (Q) and hamstrings (H) were producing rhythmically modulated posterior root–muscle reflexes. Q bursted during both phases and H reciprocally to TA. (B) Cessation of rhythmic activity by the performance of a discrete motor task, a dorsal flexion. (C) Cessation of epidurally induced rhythmic activity by plantar stimulation.

and modified by the volitional effort to perform cyclically alternating dorsal and planter flexion (Fig. 7A). Previously co-active tibialis anterior and triceps surae were with volitional interaction reciprocal, thus improving in this case the activation pattern.

When the individuals were asked to perform a volitional unilateral ankle dorsi or plantar flexion while epidurally induced rhythmic motor activity was present, the rhythmic was transformed into tonic activity (Fig. 7B). Thus, the supraspinal command overrode the network configuration induced by the epidural stimulation. We might speculate that in suprasegmental input, the lumbar cord is prioritized over the epidural stimulation by its local networks. Similar observations were made in response to reinforcement maneuvers, which also overrode the present rhythmic activities and replaced them with tonic ones. Finally, plantar stimulation during ongoing rhythmic activities interrupted the rhythmic motor activity (Fig. 7C).

Overall, from these observations, we can learn that central and peripheral inputs to segmental networks can modify the established configurations and corresponding ongoing motor activities initiated by epidural spinal cord stimulation.

CONCLUSIONS

Neurophysiological studies of motor control of spinal cord injury at first benefited from proprioceptive and exteroceptive reflex activity. Excessive reflex activity in patients with chronic spinal cord injury was shown, and the level of reflex responsiveness can be modified by habituation and dishabituation processes intrinsic to the spinal cord. Moreover, the finding that there are large variations in reflex responses and their behavior in clinically similar chronic injuries, led us to recognize that the brain excitatory influence on segmental interneurnal networks can be present below the level of the clinically complete lesion.

The main message in this review is that reflex activity elicited by single stimulus–response has significantly different motor behavior than if the stimulation is applied repetitively. The isolated lumbosacral spinal cord has the capacity to respond with a variety of patterns of motor activity. Some of the evoked patterns can be functional (e.g., extension and stepping-like activity), and some are nonfunctional (e.g., rhythmic activities with co-active bursts across all muscle groups). Furthermore, motor behavior evoked by repetitive elicitation of spinal cord reflexes also depends on the central state of excitability and clinical and subclinical residual brain motor control.

The spinal cord possesses various control capabilities even after chronic motor complete spinal cord injury. Yet when disconnected from supraspinal control, it is not able to initiate any movement. With nonpatterned repetitive input from still intact, affer-

ent structures, the spinal cord networks below the level of the lesion can be configured to perform various movements. In incomplete spinal cord injury where brain control is partially preserved, spinal cord stimulation-induced activity can be modified, controlled, and integrated. Thus, paretic and paralyzed movements in patients with chronic spinal cord injury due to upper motor neuron dysfunction have characteristic alteration of neurocontrol, which can be modified by external control of afferent input as well by residual suprasegmental brain control.

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