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Basic Concepts Underlying Activity-Dependent Mechanisms in the Rehabilitation of Sensory-Motor Function After Spinal Cord Injury

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GENERAL CONCEPTS: CONTROL OF STANDING AND STEPPING

Scientists and clinicians continue to pursue, with considerable success, interventions that can facilitate recovery of gait and other motor and autonomic functions in humans after a spinal cord injury (SCI). It is well documented that the details of the neural control of stepping and standing in quadrupeds are processed within the spinal networks that receive cutaneous and proprioceptive input, even without any input from the brain (1,2). Qualitatively, the potential for the same type of detailed control is present in the human lumbosacral spinal cord and there has been some success in humans with motor-complete SCI (American Spinal Injury Association Impairment Scale [AIS] A and B) to regain some voluntarily generated movements after more than 1 year post-injury (3–7). Some of the significant advances in achieving unassisted, full weight-bearing standing in humans with chronic (defined as more than 1 year post-injury) complete motor paralysis using combinations of interventions will be discussed. There have also been significant achievements in attaining full weight-bearing, unassisted stepping in the animal models with chronic motor-complete SCI. This goal, however, has not yet been fully achieved in human subjects. These advances and the interventions tested with the goal of improving motor function will be discussed in the chapter.

The general concept underlying the more recent advances in improving stepping and standing ability, after complete and incomplete SCI, is that the brain generates the commands to step or stand. Once the decision to stand or step is made and as long as this intent persists, most of the detailed modulation of the activation patterns of the musculature of the lower limbs, trunk, and upper limbs is controlled by the spinal neural networks. This is done largely automatically and is enabled by spinal networks processing proprioceptive and cutaneous inputs in real time. It remains unclear just how automatically the human spinal cord can perform these locomotor functions without some assistance from supraspinal centers. It is becoming increasingly evident, however, that the potential magnitude of the effect of appropriate rehabilitative (activity-dependent) strategies have largely been underestimated. For example, significant coordinated motor control can be achieved at the spinal level when there is access to the sensory input that reflects a given movement in rats, cats, and humans after an SCI.

This chapter focuses on the following two underlying concepts. First, the spinal cord is an important information-processing and decision-making center. Second, the spinal cord's processing ability is experience-dependent. The functional properties and potential of the spinal networks are shaped by the motor tasks performed. To illustrate these concepts, it is valuable to compare the theoretical models of the neural control of stepping in uninjured (control) subjects and in individuals with an incomplete or complete SCI (Figure 54.1).

After an incomplete injury at the thoracic level, some, but not all, descending axons that normally project to the lower spinal segments and motor pools are functionally interrupted at the site of the lesion(s) (8). A loss of functional synapses results in a significant change in the functional properties of both the remaining intact and the injured neurons and their synapses. Although multiple factors contribute to these changes, the adaptations and relative importance of the remaining uninjured projections and their newly formed functional connections can result in significant and rapid functional recovery. The remaining synapses that survived the initial injury are soon modified in number, size, and synaptic surface relative to their original and even novel neuronal targets (8,9). Further, without some form of use of the remaining sensory-motor network, via training or rehabilitation, these newly formed connections are likely to result in more aberrant synapses, with major implications for motor function post-injury (10).

Details of the functional changes that occur in the spinal pathways after an SCI can be shaped by the newly imposed patterns or levels of activity as a result of the injury. These activity-related changes seem to be learned

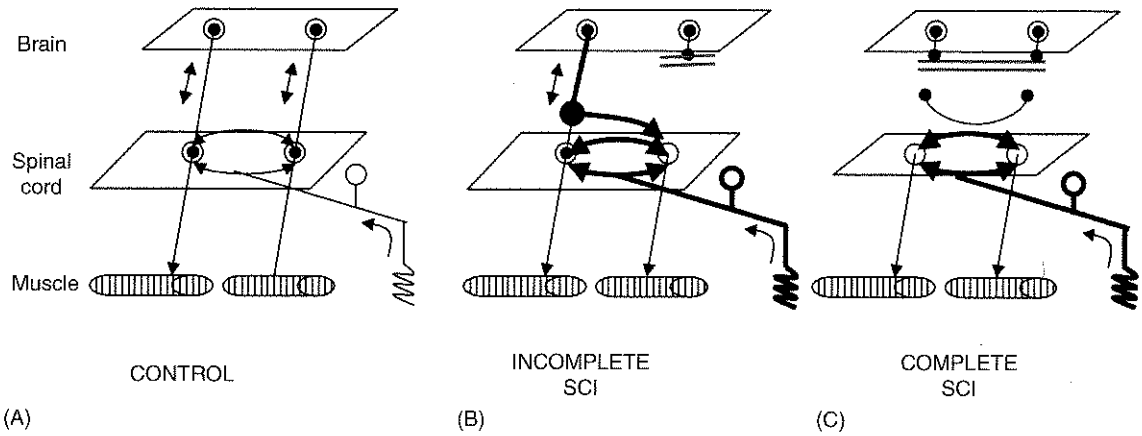

FIGURE 54.1 A general conceptual model of the control of locomotion and the adaptive events that may occur in the spinal cord after an incomplete (B) or a complete (C) disruption of ascending and descending signals to and from the brain compared to the uninjured (control) state (A). The bolder lines imply pathways that are probably at least functionally adapted after an SCI. In the incomplete model (B), both supraspinal and spinal components most likely adapt in ways that can improve function. Significant adaptations, however, also occur in the spinal cord without any input to the spinal cord from the brain (C).

SCI, spinal cord injury.

(i.e., the functionality of the pathways either can be reinforced or depressed depending on the pattern of activity that predominates). After a severe SCI, there may be little or no voluntary control of the stepping patterns, but the remaining spinal networks can be facilitated to generate stepping patterns, particularly if there are some connections that remain functional post-injury for a given period of time. Perhaps, these networks acquire the ability to function more independently of supraspinal control than normally occurs, particularly when a motor task is practiced. For example, individuals with an incomplete SCI were able to improve their stepping ability by step training without having any improvement in their voluntary control of leg movement (Figure 54.1) (4,11,12). Supraspinal changes also occur in association with step training in individuals with an incomplete SCI (13). It appears that a relatively small amount of remaining descending functional input distal to a lesion can become highly effective, probably as a result of concomitant adaptations at the spinal and supraspinal levels.

There is more than just a loss of neural function post-SCI. Muscle atrophy results in a proportional reduction in force-generating potential (14). Interestingly, the amount of atrophy that occurs differs substantially among individuals after an SCI, with no obvious explanation existing for this variability. Some may be the result of differing degrees of spasticity or medication usage, but this has not been studied carefully. Changes in the potential of muscles to generate forces also define the ability to control movements. For any level of neural function remaining, the larger the muscle fibers (or motor units) that can be recruited, the more force that can be generated (15). The degree to which we can normalize muscle mass and function after SCI remains poorly understood. In essence, our targets for recovery of movement post-spinal injury should be a combination of both training the neural control of motor tasks and recovering the potential of muscles to generate higher forces for a given level of neural control.

SENSORY INFORMATION: MONITORED AND PROCESSED BY THE SPINAL CORD

All modes of sensory input, such as from muscle spindles, Golgi tendon organs, free nerve ending in muscles, joint receptors, and skin receptors, provide information that can be used to recognize specific temporal patterns of activation associated with each continually changing phase of a step cycle or a given timepoint or level of loading while maintaining a standing posture. This sensory information seems to be sufficient for the spinal cord to "anticipate" what just happened and should happen next. What just happened is registered by the excitatory and inhibitory events that occurred immediately preceding a given timepoint. It seems reasonable to assume that the spinal cord has evolved so that its neural pathways can readily recognize appropriate patterns of sensory cues (e.g., when one leg is beginning the swing phase and the other is in the early stance phase during a step cycle). We propose that spinal networks interpret a complete or "gestalt" pattern of afferent input from the total ensemble of peripheral sensors in a dynamically appropriate pattern. In essence, this enables the spinal networks to function as a feed-forward system and thereby make context-dependent decisions in real time or in advance of a given action (16).

In effect, the ensemble pattern of sensory information projected to the spinal cord at any given instant during a step cycle provides precise information as to the kinematic and kinetic events of the lower limbs. In turn, the spinal circuitry recognizes this pattern and responds by generating the appropriate motor signals sufficient for initiating and sustaining the next phase of the step cycle (Figure 54.2) and even if the stepping requires backward or sideward stepping (Figure 54.3). When considering the millions of years of evolution of the posture and locomotor systems in a 1G environment, one can more easily understand how the spinal circuitry has been designed to routinely address and utilize the highly predictable patterns of sensory input associated with posture and locomotion. Implied within

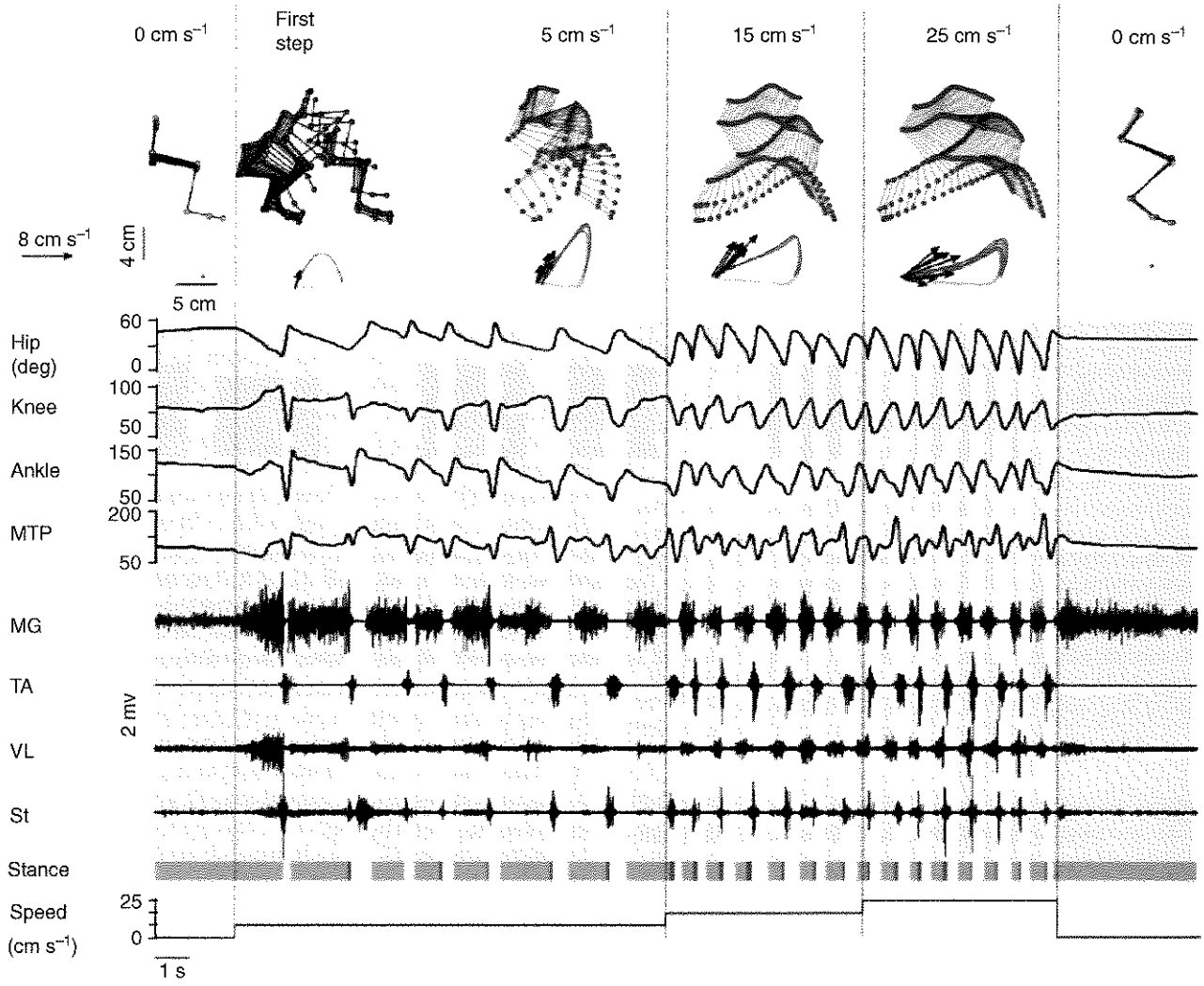

FIGURE 54.2 Effects of velocity-dependent afferent input on motor patterns. Representative example of hindlimb kinematics and electromyography (EMG) activity recorded from a continuous sequence of steps during which the speed of the treadmill belt was changed gradually (0, 5, 15, 25, and 0 cm s^{-1}).

MG, medial gastrocnemius; St, semitendinosus; VL, vastus lateralis.

Source: Adapted from Courtine G, Gerasimenko Y, van den Brand R, et al. Transformation of nonfunctional spinal circuits into functional states after the loss of brain input. *Nat Neurosci.* 2009;12(10):1333–1342. doi:10.1038/nn.2401

this concept is the likelihood that the spinal circuitry can not only correct movements in response to sensory information, but also anticipate what the correct patterns should be in normal stepping. In other words, from an engineering perspective, the spinal circuitry responds as a feed-forward control system (16).

The meaningful components of the sensory information relayed through the spinal cord during stepping or standing seem to be conceptually analogous to the alphabet, words, phrases, and sentences. For example, activation of different combinations of individual sensory receptors in a muscle might represent a "word," and information inclusive of the actions of synergists and antagonists might provide a "phrase" among joint segments. Finally, this sensory ensemble among muscles controlling all joints of both legs might send a complex pattern of information in the form of a "sentence" to the spinal cord. Thus, different combinations of sources and modes of receptor information formulate meaningful words, phrases, and sentences for the spinal cord to interpret. In response, the sequence of motor activation patterns can be generated in part by anticipating and recognizing the "words," "phrases," and "sentences" generated by an afferent input. The spinal networks may recognize not only the presence or absence of sensory input, but also the dynamics of multiple combinations of inputs. The spinal networks seem to recognize and anticipate temporal patterns and detect and correct patterns of movement and mechanical events that are inconsistent with effective stepping or "ineffective" sensory patterns.

As helpful as sensory information can be in providing a source of "control" for the spinal cord, it can also have highly undesirable consequences that must be managed. After an SCI, a common feature is the emergence of aberrant connections throughout the sensorimotor circuitry,

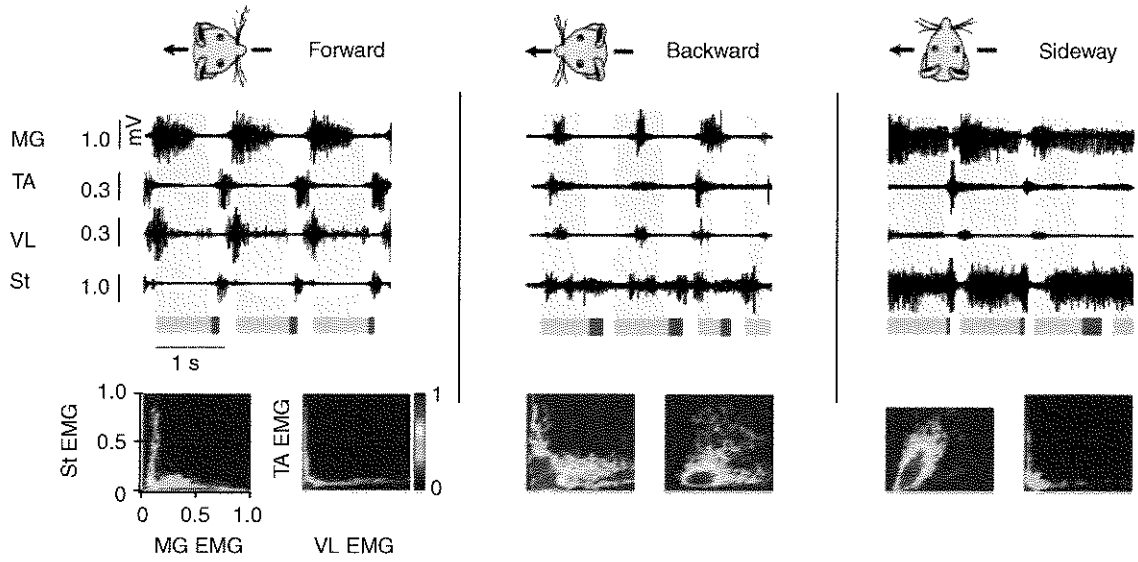

FIGURE 54.3 Effects of direction-dependent afferent input on motor patterns. Representative example of raw EMG activity during continuous locomotion in the forward, backward, and sideways directions. The same limb from the same rat is shown for the three directions, which corresponds to the leading (front) limb during sideward locomotion. Probability density distributions of normalized EMG amplitudes between the semitendinosus and medial gastrocnemius muscles, and the tibialis anterior and vastus lateralis muscles are shown at the bottom. L-shaped patterns indicate reciprocal activation between the pair of muscles, whereas line-shaped patterns indicate coactivation.

Source: Adapted from Courtine G, Gerasimenko Y, van den Brand R, et al. Transformation of nonfunctional spinal circuits into functional states after the loss of brain input. *Nat Neurosci.* 2009;12(10):1333–1342. doi:10.1038/nn.2401

whereby a given source of sensory input can "reflexively" generate uncoordinated contractions among multiple muscles, a phenomenon which falls into the category of spasticity (17). The initial and consistent response of the physician is to prescribe antispasmodic medication. For individuals with severe uncontrolled spasticity, these medications may be the only source of relief from the spasms and stiffness caused by spasticity. However, while reducing spasticity, and the associated reflex movements, the administration of baclofen also will not only reduce the amount of sensory information available to the spinal circuitry that generally controls posture and locomotion, but it can also reduce the forces generated by motor units when they are activated (18). Given that the level of voluntary supraspinal control ranging from minor to even complete is impaired after an SCI, the control that can be derived from the sensory system can become very crucial. Theoretically, thus, minimizing this sensory input via antispasmodic medications has the potential to negatively impact the performance of postural and locomotor activities. An important point here is to realize that the level and the site(s) of the excitability states of spinal networks can limit movement control by being too little or too great. Each individual, in consultation with his/her physician and caregivers, should be aware of the trade-offs of either state, both in the immediate and in the very chronic stages of antispasmodic medication.

Apart from antispasmodic medication, another frequently used strategy to eliminate spasticity is to induce paralysis at the level of the neuromuscular junction with intramuscular injections of botulinum toxin, with the effect lasting several months. As a result of the absence of activation and any force generation, the muscles injected will atrophy severely and rapidly. Thus, either of these interventions to minimize spasticity may have negative consequences in subsequent efforts to regain the ability to stand or step post-injury.

Thus, a decision must be made as to whether or not to use an interventional strategy to take advantage of the sensory input to the spinal cord by providing intermittent load-bearing exercise in the form of standing and/or stepping or to minimize the sensory effects at the expense of losing some motor function. The choice becomes one of the tolerating disruptive and spontaneous contractions while trying to maximize the functional potential of the spinal circuitry versus the convenience of suppressing spontaneous contractions. The strategy chosen should be based on a discussion—between the patient and the physician—regarding all of the advantages and disadvantages in the context of both short- and long-term consequences and the goals of the subject.

Although one need not assume that all afferent input associated with stepping will be precise at every instant, the more closely the pattern of input approximates normal stepping, the more likely the stepping patterns will be executed effectively and successfully. In more severely injured individuals, there are fewer neural control options available for stepping, making it more critical for the remaining sources of sensory information to function effectively in guiding a motor response (i.e., to match the input normally associated with load-bearing stepping). As noted earlier, the afferent input to the spinal cord (and to the brain, if the injury is incomplete) after an SCI generates a new, or at least a modified, "experience." The newly acquired properties of the spinal cord will reflect the sensory experience during and after the period of spontaneous anatomical and functional reorganization that occurs after an SCI and will be important in functional outcomes and treatment efficacy.

CENTRAL PATTERN GENERATION: SPINAL CORD CONTROL OF LOCOMOTION

Up to this point, we have emphasized the importance of sensory information processing to generate stepping. The same neurons that perform the central processing of sensory information as discussed above, however, can generate coordinated and alternating flexion-extension movements in the SCI subjects. This occurs by the peripheral activation of appropriate mechanosensors of the lower limbs bilaterally, as occurs during locomotion in uninjured subjects. By definition, central pattern generation is the generation of these alternating pattern outputs from motor nerves without sensory input or supraspinal input (Figure 54.4A and B). One can surgically isolate the lumbosacral spinal cord from supraspinal and rhythmic sensory input of a mouse, rat, or cat and induce repetitive steplike patterns by administering one or more of a number of pharmacological agents (serotonergic, noradrenergic, and dopaminergic agonists and glycinergic and GABAergic antagonists) associated with neurotransmitters involved in the motor output of these spinal segments (1,19–21). Repetitive steplike cycles can be generated for hours by networks of neurons without any phasic descending or afferent input. This cyclic generation of a steplike pattern is called *fictive locomotion* (Figure 54.4B). Although the level of activation of a motor pool can vary from cycle to cycle, the motor output cannot be matched to the external environment or any kinematics or kinetics events of the limbs because there is no afferent feedback from the periphery. To generate successful load-bearing stepping and standing, afferent information must be available to the spinal cord. Thus, an important functional property of some of the same spinal pathways that generate fictive locomotion is the ability to effectively process the sensory information associated with the continuously changing phases of the step cycle (Figure 54.2).

HOW SMART IS THE SPINAL CORD? EVIDENCE FOR COMPLEX SENSORY AND MOTOR PROCESSING

What do we mean when we say the spinal cord is *smart?* We use the term here to emphasize that the spinal cord can process sensory information in the context of the combination of events occurring at any given time, that is, the physiological state. We often refer to this as "state-dependent processing," reflecting the ability of the spinal cord to "decide" how to respond to a given sensory input. For example, a given pattern of sensory input can be processed (interpreted in real time by the spinal pattern-generating networks) such that ipsilateral flexion and contralateral extension can be generated in the hindlimbs when the dorsal surface of the foot is mechanically perturbed during the swing phase of a step. If the same stimulation is applied during the stance phase of that same limb, however, then an ipsilateral extension and contralateral flexion response will be induced (22). Thus, the spinal cord interprets the stimulus differently, depending on the phase of the step cycle. These are examples of effective processing of neural inputs that illustrate the useful "decision-making" abilities of the spinal cord because both of these responses are positive adaptive events that increases the probability that stepping continues with minimal disruption. This real-time neural processing that can generate the necessary mechanical outcome largely due to robust feed-forward mechanisms within the spinal networks controlling posture and locomotion (16).

Numerous examples exist in animals and in humans that illustrate that the spinal cord responds to proprioceptive input in a "state-dependent" manner. One of the most functional illustrations of this phenomenon is when the level of loading on the limbs during stepping is altered. For example, in individuals with a complete SCI, the level of activation of extensor muscles increases as the level of loadbearing increases (3). A similar response to loading has also been observed in nondisabled and incomplete SCI subjects (Figure 54.5A). This load-dependent phenomenon is also present during spinal neuromodulation in individuals that have been motor complete for more than a year (Figure 54.5B). Load-dependent modulation in individuals with motor-complete SCI are also present during stand training when stimulating the spinal cord with a constant intensity, wherein the motor output during standing changes as a function of the level of loading (Figure 54.5B). In this example, the spinal network begins to generate an alternating electromyographic (EMG) bursts at the higher loads. In most cases, these responses to loading intuitively appear "teleologically correct," in the sense that it would seem to be an advantage for the response to loading to be automatic or programmed in the lower (spinal cord) control circuits.

CAN THE SPINAL CORD LEARN A MOTOR TASK? REPETITIVE PRACTICE IMPROVES GAIT

In adult cats whose spinal cords were surgically transected at a mid- or low-thoracic level, the ability to step or stand is a function of whether these motor tasks are practiced (1, 23–25). If adult spinal cats are trained daily to step with full load-bearing on a treadmill over a period of 3 to 12 weeks, then their stepping ability improves. If they are trained daily to stand, then their standing ability is improved. The specificity of this training or experience is illustrated by the fact that the animals trained to stand will learn to stand, but their stepping ability remains poor or even worsens. The most effective rehabilitative strategy for training stepping and standing after SCI and during the same training period has not been studied in detail, but these types of experiments are being conducted in both animals and humans. Given our capability to routinely include training that focuses both on the ability to stand and to step, it seems likely that the spinal circuitry can learn to effectively generate standing and stepping at the same time. While preliminary data seem to support this outcome, the question as to what the training and other interventional protocols should be and when both motor tasks should be trained is as yet unanswered (Figure 54.6). Two other features of learning are present in trained spinal animals. If step training is stopped, their ability to step declines over a period of weeks, as if the spinal circuits "forget" how to perform the motor task. If these same spinal animals then are retrained to step, they learn to step much more quickly than when trained the first time after the SCI. This response is another learning-related phenomenon (i.e., relearning a motor task occurs faster than during initial training) (20,26). Similar studies have been and are still being performed in humans

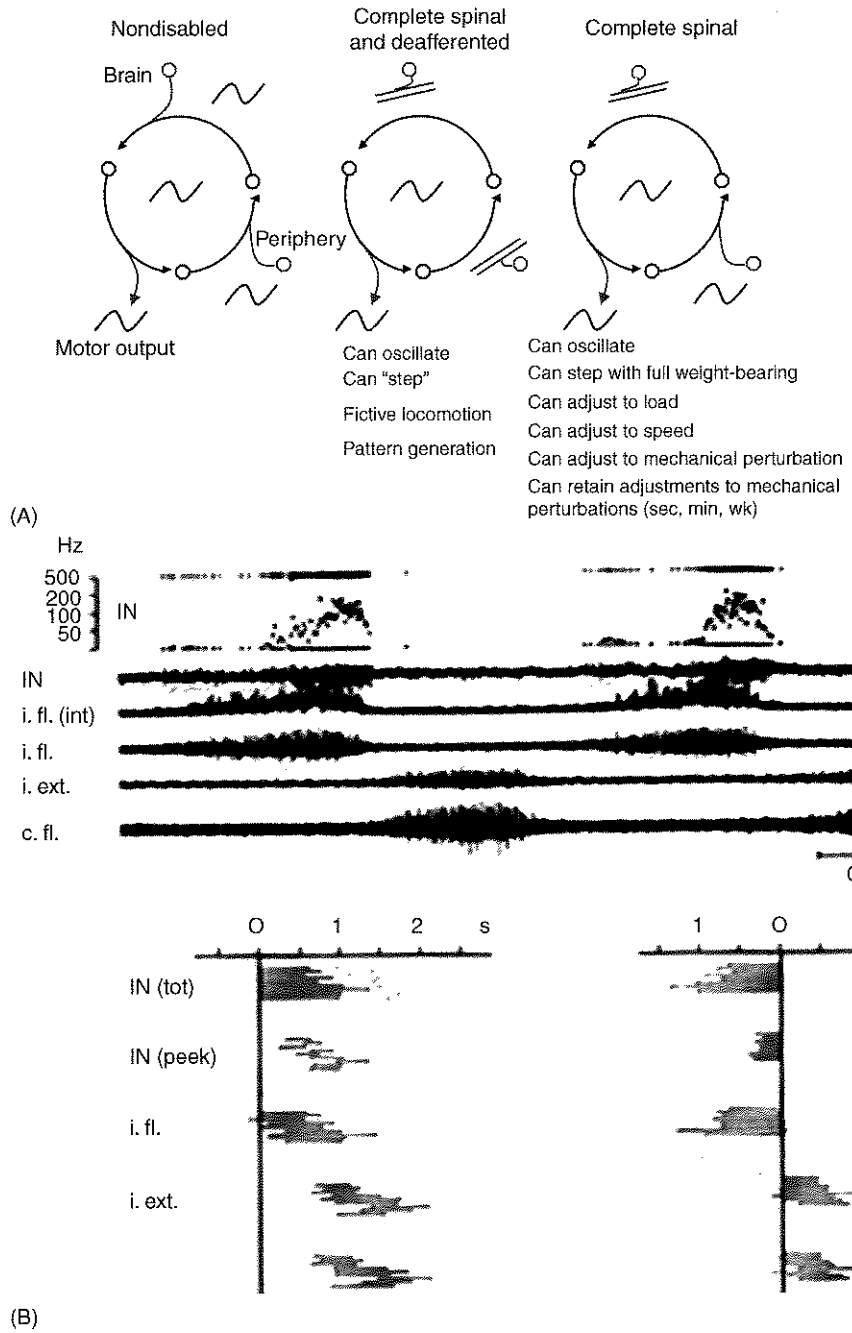

FIGURE 54.4 (A) Conceptual models of the spinal circuitry in a nondisabled, a spinal isolated (no supraspinal or peripheral afferent input to the spinal cord), and a complete spinal (elimination of supraspinal connections only) animal are shown. Some of the functional capabilities of the two injury models are listed below, indicating the much greater functional capacity when the afferents are intact. (B) Interneuron (IN) activity during central pattern generation. Lumbar (L7) interneuron activity as well as efferent activity in ipsilateral (i.) and contralateral (c.) flexor (fl.) and extensor (ext.) muscle filaments recorded in a spinal curarized cat injected with dihydroxyphenylalanine (DOPA) and Nialamide. The timing of activity within different muscle filaments for 10 consecutive cycles and the pattern of modulation of the interpulse intervals of an IN during these 10 cycles are shown. In the left graph, the cycle starts with the onset of activity in the IN and in the right graph the zero point is moved to the end of the IN burst. It can be seen that the termination of activity in the IN is related tightly to the termination of the fl. burst. i.fl is the flexor motor filament recording and i.fl (int) is the signal rectified; IN (tot) and IN peak indicate the total duration of the activity and the peak frequency within a cycle, respectively.

Source: Adapted from Edgerton VR, Grillner SA, Zangger P. Central generation of locomotion in vertebrates. *Neural Control Locomotion.* 1976:439–464. doi:10.1007/978-1-4757-0964-3_18

with an SCI (27). It appears that the essential learning features described above for laboratory animals also apply to humans.

Greater gains in performing a specific motor task after an SCI occur when that motor task is practiced compared to when there has been no or limited practice. Thus, it seems that motor training should be considered in concert with newly developing interventions designed to repair or regenerate tissue via growth factor modulation, cell implants, and so forth (28). If the spinal cord pathways are not trained

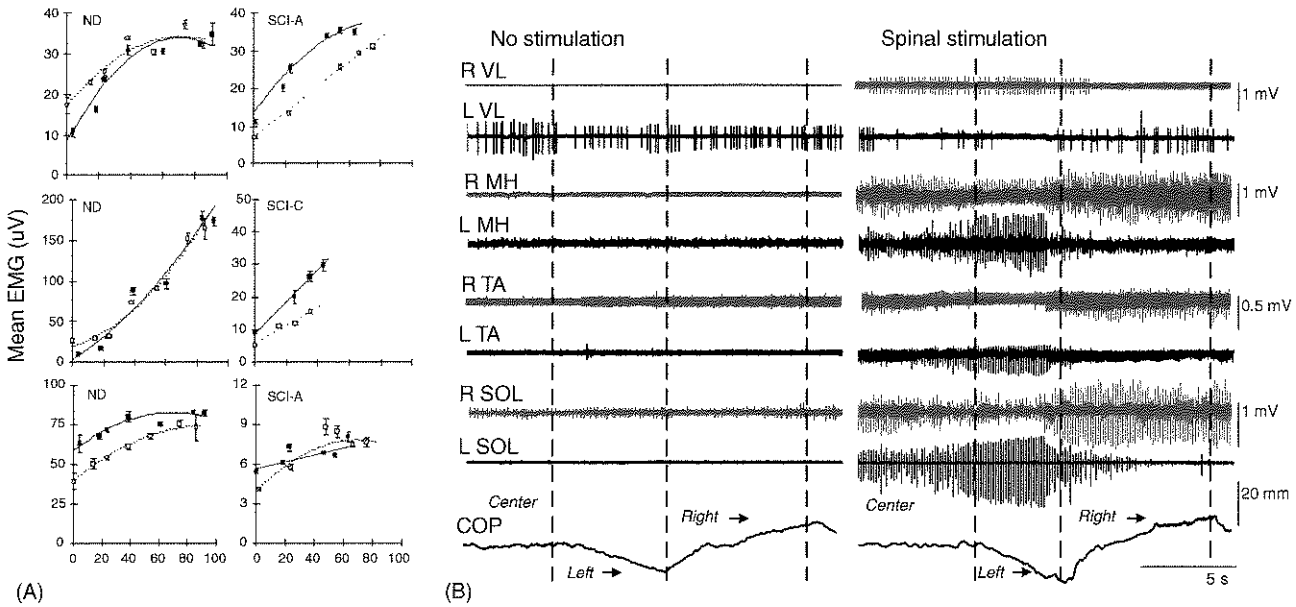

FIGURE 54.5 (A) Data from multiple series of steps taken at different levels of loading, as regulated by a body weight support system, are shown. Exemplary data from a nondisabled (ND) subject and from SCI subjects are shown. In general, extensor and flexor EMG activity increased with higher peak limb loading conditions independent of the level of available supraspinal input. Averaged soleus (top), medial gastrocnemius (middle), and tibialis anterior (bottom) surface EMG mean amplitude per burst (μ, V; rectified, high-pass-filtered at 32 Hz) versus limb peak load (percent of body weight load, % BWL) from ND, clinically incomplete (SCI-C) and clinically complete (SCI-A) subjects. Each point represents the average of EMG mean amplitudes (±SEM) within a 10% interval of the BWL range (0–10, 10–20%, etc.). Data from the right limb (open symbols) and left limb (closed symbols) of each subject are shown separately. (B) Modulation of EMG activity in the leg muscles and the center of pressure (COP) signal during self-initiated body weight displacements in the mediolateral directions in a participant with SCI (AIS A, T9, 2 years post-injury) without and in the presence of spinal stimulation delivered at the lumbosacral area with frequency of 15 Hz and at intensity of 60 mA. The directions of the body weight displacements are highlighted in gray and are indicated on the top. Note pronounced activity of the ipsilateral muscles during weight-bearing on a given side, enabled by spinal stimulation.

EMG, electromyogram; HM, medial hamstring; SEM, standard error of mean; TA, tibialis anterior; VL, vastus lateralis.

Source: Adapted from Harkema SJ, Hurley SL, Patel UK, et al. Human lumbosacral spinal cord interprets loading during stepping. *J Neurophysiol.* 1997;77(2):797–811. doi:10.1152/jn.1997.77.2.797; Adapted from unpublished data, Sayenko et al., 2017.

to step, then new functional connectivity via incorporation of new or modified cells may not become functional. In general, it seems likely that greater recovery in motor function after an SCI will occur by combining the interactive or complementary effects of multiple interventions. At the same time, it is possible for the activity-dependent changes from one intervention to interfere with the training effect for another intervention. For example, it has been reported that initiation of an activity-dependent rehabilitative strategy immediately after a brain injury can result in less recovery than will occur without any such treatment (29). In general, activity-dependent interventions potentially can induce cellular and systemic modulation in either a negative or a positive direction, as can any specific pharmacologic intervention, for example. Thus, more is not always better and optimizing the timing of an intervention and its intensity of training for a given subject will always be an issue requiring careful attention. It seems likely that too many stressors can be imposed for any physiological system to adapt to simultaneously, particularly after a severe SCI (30,31).

NEUROPLASTICITY: SPINAL AND SUPRASPINAL CONTROL SYSTEMS

As noted previously, some recovery has been reported in individuals who have some residual descending input post-SCI. A published case report of a four-and-a-half-year-old child with C5 SCI, which left only a small amount of preserved cord tissue dorsally and ventrally, illustrates how intensive locomotor training may have value for some pediatric clients with motor-complete SCI. The child, who was nonambulatory and wheelchair-dependent, received locomotor training for 76 sessions, beginning 16 months after SCI (32). After 1 month of locomotor training, the child was able to use his legs for community ambulation using a rolling walker. By the end of the training period, an average of 2488 community-based steps per day and a maximum speed of 0.48 m/s were obtained. In a 1-month follow-up after the completion of 76 sessions, the level of performance was sustained, and the preferred walking speed had increased significantly beyond that recorded at the end of training. These changes occurred in spite of no change in the clinically defined lower extremity motor scores, that is, there was no change in the level of voluntary control. The child went on to attend kindergarten full time using a walker. Although this is a case study, it points out several important issues. First, the level of reorganization that can occur both supraspinally and spinally within the sensorimotor system is far greater than usually assumed. Second, the number of therapy sessions needed to initiate and continue to improve motor function is significantly more than is generally allowed for reimbursement in the

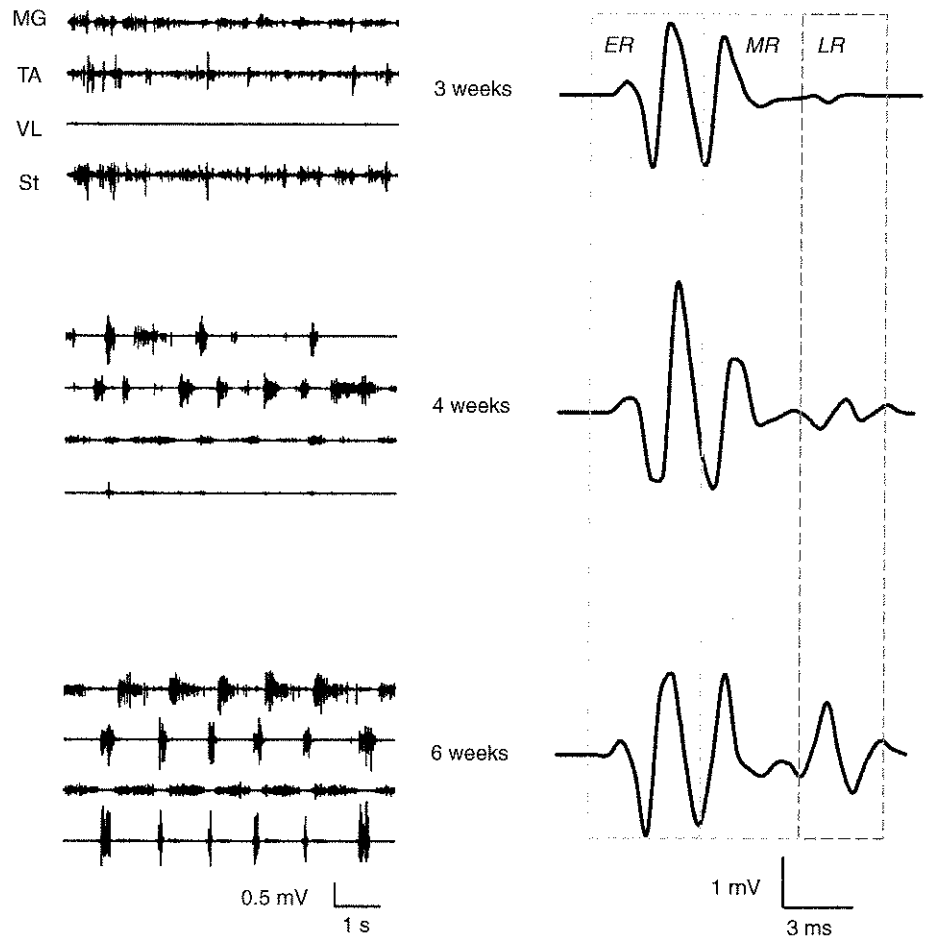

FIGURE 54.6 EMG patterns of the MG, TA, VL, and St muscles at 3, 4, and 6 weeks post-ST during stepping induced by epidural stimulation (40 Hz) at S1 (A). Note the more robust and consistent EMG burst patterns at 6 weeks compared with 3 and 4 weeks. Representative ER, MR, and LR from the TA muscle at 4.5-V stimulation 3, 4, and 6 weeks after ST are shown in (B). Note that the LR is minimal at 3 weeks and progressively increases from 4 to 6 weeks.

EMG, electromyogram; HM, medial hamstring; SEM, standard error of mean; TA, tibialis anterior; VL, vastus lateralis.

Source: Adapted from Lavrov I, Gerasimenko YP, Ichiyama RM, et al. Plasticity of spinal cord reflexes after a complete transection in adult rats: relationship to stepping ability. *J Neurophysiol.* 2006;96(4):1699–1710. doi:10.1152/jn.00325.2006.

U.S. healthcare system for a given patient. Regardless of the economic issues, these observations point out the importance of knowing which individuals with a given kind and severity of SCI can be expected to improve and to what level they can improve when given proper postural and locomotor training, i.e., activity dependent experience.

Based on the postmortem analysis of individuals with long-term SCI, it was concluded that a high level of motor control seems possible with relatively few descending axons extending below the level of the lesion (33). Rhesus monkeys have been shown to regain very effective bilateral locomotor function within 3 months after a unilateral thoracic corticospinal tract lesion (34). As suggested earlier, all of these observations probably reflect a synergistic effect of adaptive responses in the spinal cord and supraspinal motor control centers. The ability of motor control centers in the brain to adapt after an SCI is dramatic. It appears that the brain has the ability to reorganize itself so that novel pathways can control movement as a result of the combined and concomitant adjustments occurring at the supraspinal and spinal levels (10).

ENHANCING INFORMATION PROCESSING PHARMACOLOGICALLY WITHIN THE SPINAL CORD TO IMPROVE MOTOR OUTPUT

Another approach on the horizon is the administration of adrenergic and serotonergic agonists to the lumbosacral spinal cord segments to facilitate locomotion. Activation of either the adrenergic or serotonergic neurotransmitter system can generate fictive locomotion in cats and rats (2,35). In the lumbosacral spinal cord of uninjured individuals, the only effective source of these transmitters is from the synapses of axons descending from supraspinal neurons. After a motor-complete SCI, little or no noradrenaline (NA) or 5-hydroxytryptamine (5-HT) persists in the spinal cord. It is assumed that following severe SCI, the presynaptic terminals of 5-HT neurons degenerate but postsynaptic receptors on neurons remain. The effects of administration of serotonergic agonists attribute to the influence of these drugs on postsynaptic receptors at spinal level (21). When chronic spinal animals are given an agonist of these neurotransmitters, however, locomotion is improved in some

animals but depressed in others. Although the explanation for this variability is not fully understood, it probably reflects the highly dynamic feature of the responsiveness of the spinal cord, often referred to as the "physiological state" (36), which can change over time. For example, NA agonists can effectively modulate the spinal locomotor circuits via the depression of the excitability of polysynaptic circuyiries (19), which play a determinant role in enabling locomotion with electrical stimulation (37–40).

Multiple types of 5-HT receptor-specific modulators can influence locomotion of spinal rats facilitated by epidural spinal cord stimulation. Combined activation of serotonergic, noradrenergic, and dopaminergic receptors when used in the appropriate proportions can positively modulate the quality of the kinematic features of coordinated weight-bearing locomotion in adult spinal rats (Figure 54.7) (19).

From a clinical viewpoint, there are some practical challenges to pharmacologically facilitating stepping (41). We have little understanding of how NA or 5-HT modulates sensory processing within the spinal cord under in vivo conditions. A wide range of pharmacological interventions might be helpful in enhancing motor output. Glycine is a major inhibitory neurotransmitter in the spinal cord, playing a role in the reciprocal inhibition of antagonistic motor pools via INs. Experiments in spinal cats (20) and

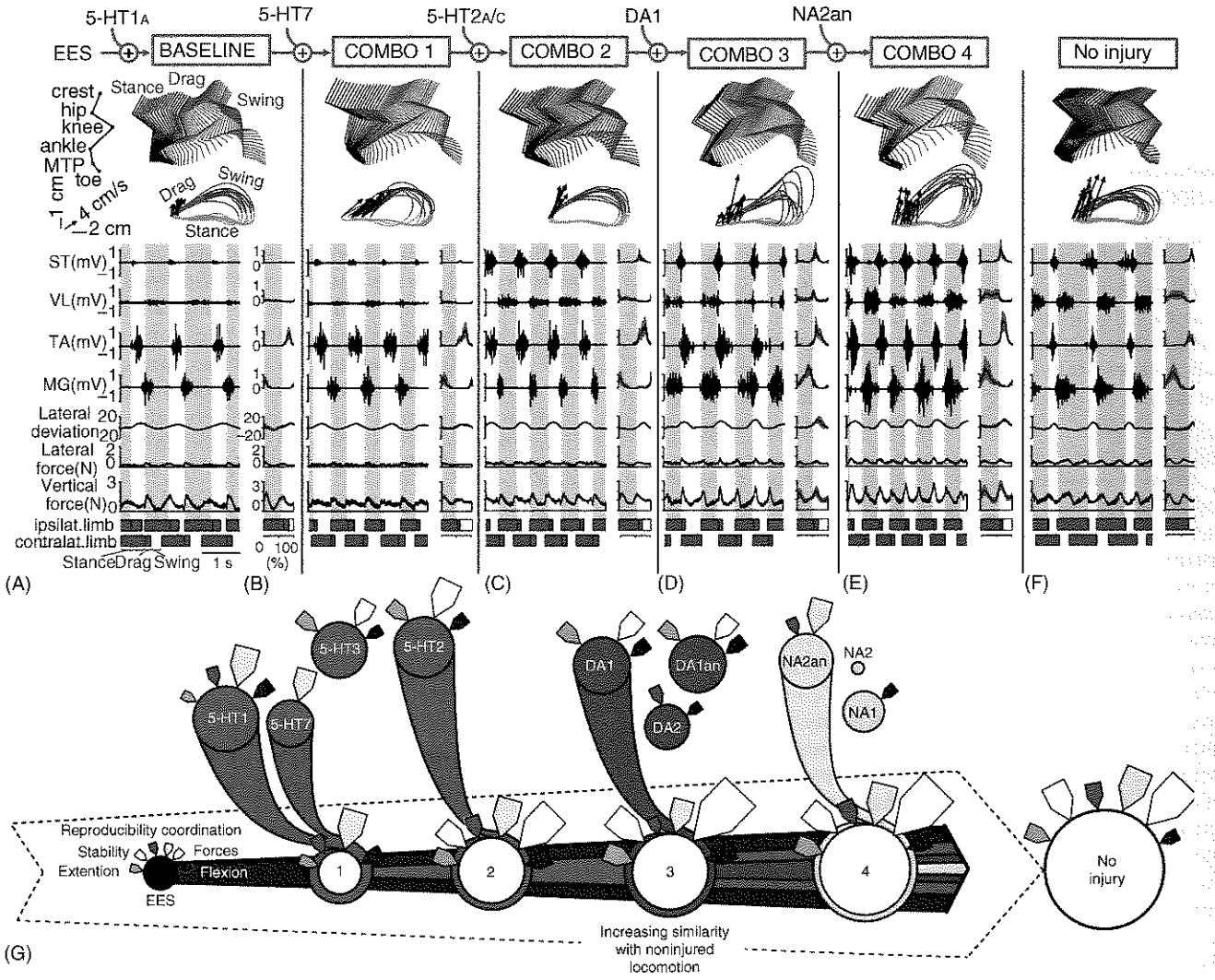

FIGURE 54.7 Multiple monoaminergic modulation of a stepping pattern in adult spina rat. Representative features of gait patterns recorded during locomotion enabled by epidural stimulation and modulated by increasingly complex combinations of agonists and antagonists to 5-HT, DA, and NA receptor subtypes are shown. (A–F) From left to right, the successive panels show locomotor features resulting from manipulating one additional monoaminergic pathway compared with the previous panel as indicated above each panel. EMG activity from proximal and distal muscles and changes in whole-limb oscillations and ground reaction forces in the mediolateral direction are displayed. Representation of receptor-specific tuning function and their interactions. The size of each circle is proportional to the respective ability of each serotonergic, dopaminergic, and noradrenergic receptor subtype to modulate gait features toward those underlying locomotion of healthy rats (rightmost circle). This schematic representation highlights that each of the investigated monoaminergic pathways show the ability to tune unique locomotor subfunctions with distinct modulatory amplitude and that these tuning functions can sum when manipulating multiple pathways simultaneously.

Source: Adapted from Musienko P, van den Brand R, Märzendorfer O, et al. Controlling specific locomotor behaviors through multidimensional monoaminergic modulation of spinal circuitries. *J Neurosci.* 2011;31(25):9264–9278. doi:10.1523/JNEUROSCI.5796-10.2011.

rats (40,42) suggest that modulation of inhibitory pathways can be used to improve locomotion. In spinal cats that were trained to stand and could not step, strychnine facilitated stepping when the animal was placed on a treadmill. Strychnine seemed to facilitate information processing rather than directly inducing steplike oscillations. Perhaps analogous drugs can be developed so that this approach can be used in humans.

Although improvements in locomotion have been achieved using pharmacological interventions in laboratory animals, in virtually all cases, variation in responses will reflect the different pharmacological receptors and where the neurons are located that have a given receptor type as well as the dose of the drug administrated. In all cases, the side effects of drugs that manipulate these neurotransmitter systems can make their use clinically prohibitive. This might be expected for 5-HT and NA, unless the dosages can be very low and localized, given the ubiquitous nature of their distribution throughout the nervous system.

REHABILITATION GOALS AND SKELETAL MUSCLE: ATROPHY PREVENTION AND REVERSAL

The motor output of any given muscle at any given time is largely a function of both the number of activated motor units within a motor pool and the total cross-sectional area of all of their associated muscle fibers. Within a few weeks after an SCI, muscles are likely to have atrophied (43). Interestingly, however, the severity of the atrophy varies significantly among subjects and muscle groups within a subject (44,45). The reasons for this varied response are poorly understood.

Muscle atrophy can be a limiting factor in regaining mobility simply because the reduction in force output is at least proportional to the loss in muscle mass, and it is usually much greater. For example, if there is a 50% loss in muscle mass and muscle fiber cross-sectional area, and assuming no other changes, then there will be at least a 50% loss in the force that can be generated (46). Although only a small proportion of a muscle's force potential is needed when walking, severe muscle atrophy can preclude effective mobility. Indeed, one normally only activates a small proportion of the motor units within a given motor pool to walk at a comfortable speed, but if there is a 50% atrophy of all fibers in a muscle, then those motor units that are recruited will generate half the normal force that would have been generated without atrophy. This effect alone may be sufficient to prevent a subject with an SCI from executing a motor task, such as stepping or standing (47).

To walk "normally" after 50% muscle atrophy, more motor units will have to be recruited to generate the same kinematics and kinetics of a given movement. For example, a subject with 50% muscle atrophy might have to recruit 40%, as opposed to the normal 20%, of his motor units to generate the force needed to step (Figure 54.8A). The recruitment of additional motor units in each of the contributing motor pools has consequences with respect to the onset of fatigue, because the higher threshold units are more fatigable (Figure 54.8B). The larger motor units with higher thresholds for excitation have lower levels of metabolic support via oxidative phosphorylation and have a lower potential to sustain metabolic homeostasis than do the smaller, lower threshold units. Thus, in addition to regaining neural control of movement, an additional rehabilitative strategy to maximize motor performance should also include methods to recover muscle mass.

How can we prevent or minimize muscle atrophy? Some combination of electrical stimulation, treadmill training, diet, and use of anabolic growth factors could contribute to the preservation of muscle mass after an SCI. Some gains in muscle mass have been observed with electrical stimulation of a muscle. These gains are observed only when the conditions are appropriately controlled, and marginal or no improvement in muscle mass and strength is likely to occur when there is minimal or no load imposed when the muscles are activated.

If the muscles in persons with SCI are loaded (generating high forces) when stimulated, then significant muscle mass can be preserved (48,49). Subjects trained on a treadmill using body weight support training show an increase in muscle mass as indicated by magnetic resonance imaging (MRI)–derived muscle volume measurements after step training (50,51). The development of an effective way to avoid or to minimize muscle atrophy after an SCI could have a very significant effect on the motor tasks that can be performed.

Beyond muscle atrophy, it is also clear that muscle phenotypes change after an SCI, with an increase in the percentage of muscle fibers expressing fast myosin phenotypes in both laboratory animals and human subjects (43). The functional consequences of this change in phenotype are not clear, but theoretically this could make the muscles more fatigable and less efficient in generating force per unit of adenosine triphosphate (ATP). Locomotor training and muscle stimulation can also reduce the magnitude of the transition to expression of faster myosin isoforms and less slow myosin after an SCI (50,51). Muscle inactivity also has metabolic consequences, and these effects have been linked to a greater probability of developing type II diabetes and/or insulin resistance (49). But as with minimizing the atrophic effects on muscle, elevating muscle activity level can also reduce the probability of becoming insulin resistant (Figure 54.8C).

ACTIVITY-DEPENDENT SPINAL NEURAL NETWORK REORGANIZATION AFTER SCI

Behavioral and electrophysiological changes occur after a complete mid-thoracic spinal transection during step training (40,52). With repeated exposures to a training paradigm, stepping can be performed much more effectively. As the stepping pattern improves, there are concomitant changes in the pattern of the spinally evoked potentials generated during stepping. The short and longer latency responses can be observed in the beginning phase of training but with continued training the amplitude of the responses increases as do the early responses. But perhaps the more important change in the electrophysiological properties is the much greater increase in the late responses. Unlike the early repose, the late responses are much more randomly dispersed. One interpretation of this asynchronous response is that it reflects a more dominant involvement of the INs that form the neural networks that project to the

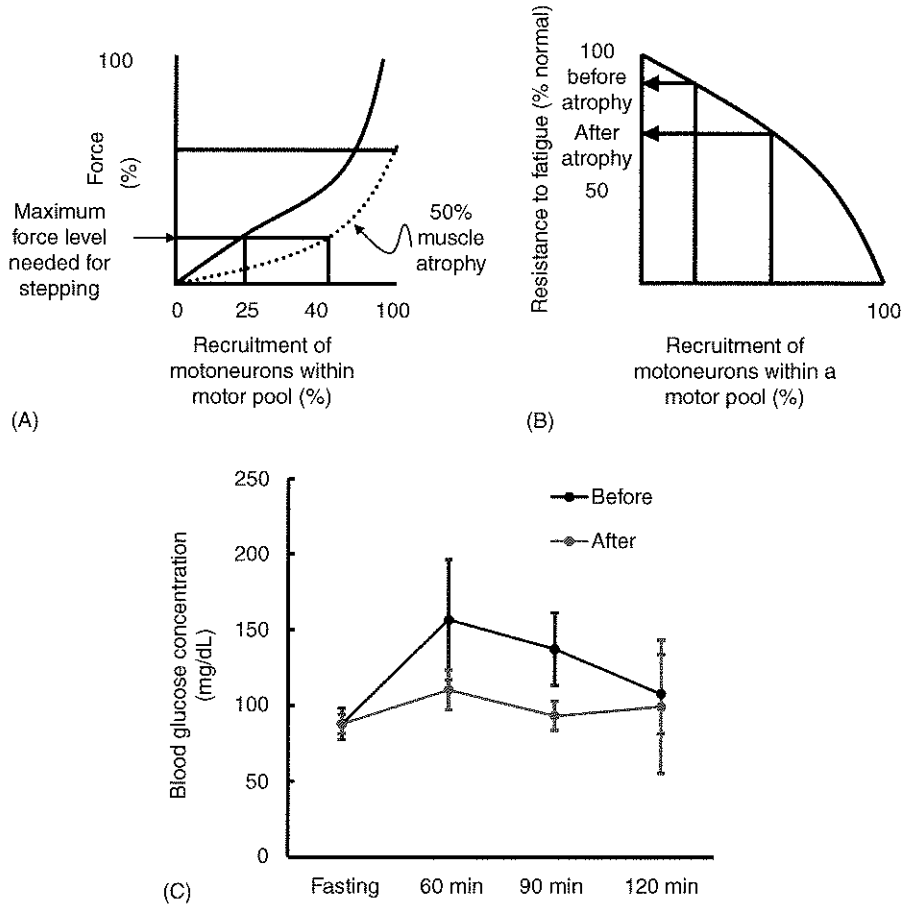

FIGURE 54.8 The theoretical relationship between the percentage of motoneurons recruited within a given motor pool and the net force that can be generated by those motoneurons recruited (A). Note the nonlinear increase in force with recruitment because, in general, the smaller motor units are recruited before the larger motor units. When the muscle atrophies, the same percent recruitment generates less force. Thus, to accomplish a given task, more units must be recruited in the atrophied muscle. The larger motoneurons recruited the latest (having a higher threshold level) also are the most fatigable. (B) Therefore, when more motor units are required to perform a task, the population as a whole will be more susceptible to fatigue. (C) Mean±SD blood glucose concentrations before and after resistance exercise training at fasting, 60, 90, and 120 min after oral glucose challenge.

Source: Adapted from Mahoney ET, Bickel CS, Elder C, et al. Changes in skeletal muscle size and glucose tolerance with electrically stimulated resistance training in subjects with chronic spinal cord injury. *Arch Phys Med Rehabil.* 2005;86(7):1502–1504. doi:10.1016/j.apmr.2004.12.021.

motor pools. This more asynchronous pattern more closely resembles the bursting EMG pattern that occurs in the uninjured state. It seems obvious that a greater complexity of the spinal networks that are engaged with repetitive step training can be driven entirely by proprioceptive and cutaneous input (53).

REGAINING VOLUNTARY CONTROL OF RHYTHMIC STEPPING PATTERN AFTER COMPLETE MOTOR PARALYSIS

The spinal networks in humans with motor-complete SCI are responsive to neuromodulation using a novel noninvasive transcutaneous spinal cord stimulation strategy. The effects seem to be similar in most respects to that achieved by stimulation with implanted epidural electrodes. For example, when trained and exposed to transcutaneous spinal cord stimulation, subjects with chronic motor-complete SCI have regained the ability to stand independently and to voluntarily move the lower limbs. The most recent results demonstrate that completely paralyzed subjects can generate bilateral stepping in response to lumbosacral spinal stimulation and when positioned in a neutral gravity position, and lying on the side with the legs supported from the ceiling (54). Also, as reported with epidural stimulation, the subjects reported an improvement in a variety of autonomic functions (4). Unlike epidural stimulation, with the noninvasive transcutaneous stimulation, several subjects showed some voluntary influence in the generation of stepping pattern in the first treatment session. There were significant improvements in rhythmic stepping patterns in all subjects during treatments (once a week) when voluntary effort was made in the presence of stimulation. The mean range in knee joint rhythmic movement generated with voluntary effort without stimulation was 40° at a cycle rate of 0.5 to 1 Hz. After 18 treatments, the mean amplitude of the rhythmic stepping movements was as great with voluntary effort alone as it was when combined with stimulation. This result demonstrates strong activity-dependent effects in the reorganization of not only the spinal networks but as importantly, it also demonstrates a rather remarkable reorganization of the descending systems from the brain. In addition,

these results demonstrated that novel supraspinal networks had developed functional connections that not only could generate alternating movements of the lower limbs, but they also demonstrate effective coordination of the motor pools across joints within each limb but also alternating bilateral coordination of motor pools (55). These results also show that with training, the functionality of these novel supraspinal–spinal connections develop a significant level of independence of electrical neuromodulation. For example, the rhythmic movement that could be generated voluntarily in the absence of stimulation during a training session was as great as it was when voluntary movement was made in the presence of stimulation (Figure 54.9).

ELECTRICAL NEUROMODULATION FACILITATES LOWER URINARY TRACT FUNCTION IN CONJUNCTION WITH LOCOMOTOR TRAINING IN BOTH HUMAN AND ANIMAL SUBJECTS POST-SCI

Significant progress has been made using activity-based locomotor training paradigms facilitated by electrical and/or pharmacological neuromodulation of spinal networks to improve autonomic as well as stepping function in both animal (2,19,38,56–59) and human (4,5) subjects. In four human subjects with motor-complete SCI implanted with a spinal cord electrode array, improved bladder function, along with cardiovascular, thermoregulation, and sexual function was reported. These results are consistent with there being an overlap of the neural circuits controlling locomotor and lower urinary tract function. Animal studies have since begun to address the potential interactions between the motor and autonomic functions in response to locomotor training. It was also shown that spinal networks can be electrically stimulated to trigger bladder emptying within seconds of the onset of the stimulation (60).

The specific physiological responses generated with spinal stimulation, however, are highly dependent on the "physiological state of all systems," that is, whether the bladder is empty or filled. The changing EMG patterns produced by a spinal rat stepping on a treadmill under the influence of neuromodulation several seconds prior to and during voiding also illustrates the state dependence of and interaction of circuits controlling stepping and bladder function. The EMG pattern transitions from a smooth, robust bipedal stepping to uncoordinated a stepping with shorter steps a few seconds prior to voiding. Stepping becomes even more disrupted (increased phase difference between the left and right hindlimbs) during voiding (Figure 54.10). As the rat changes from prevoiding to the voiding stage, the lumbosacral spinal circuitry

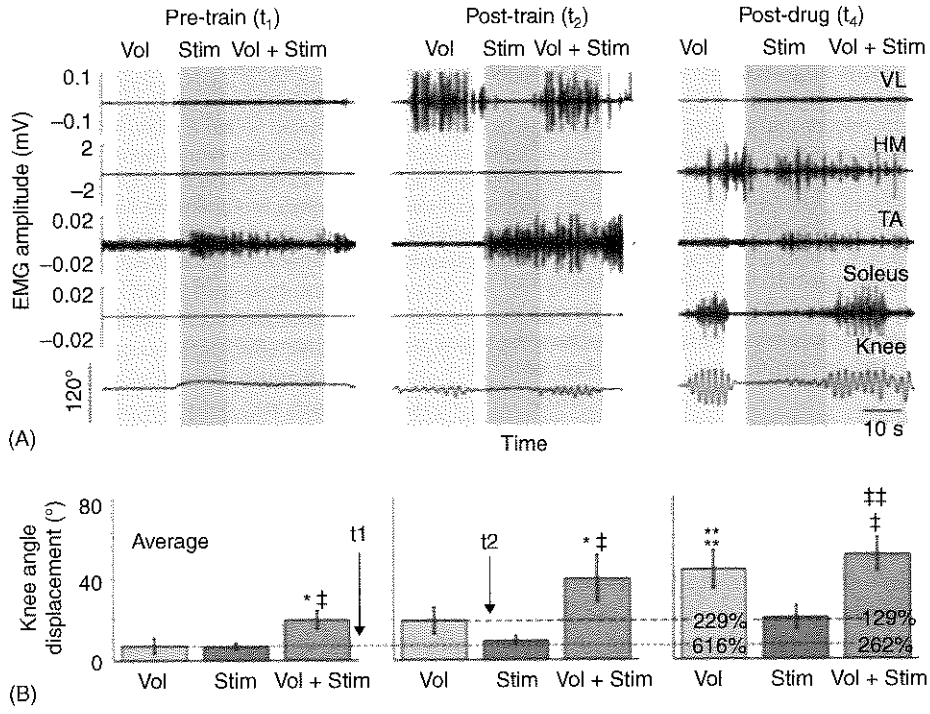

FIGURE 54.9 Voluntary control of leg movements enabled by electrical and pharmacological stimulation and training. (A) VL, HM, TA, and soleus raw EMG and angular displacement at the knee during leg oscillations with a voluntary effort alone (Vol), stimulation at T11 (Stim), and Vol+Stim at the Pre-Train (t1), Post-Train (t2), and Post-Drug (t4) phases. (B) Mean±SEM (n = 5 subjects) knee angular displacements at the Pre-Train (t1), Post-Train (t2), and Post-Drug (t4) phases under each experimental condition described in (A) with stimulation. The dashed horizontal lines indicate the mean voluntary effort at t1 and t2, respectively. The percentiles at t4 reflect differences between t4 and t1 (616% & 262%) and t4 and t2 (229% & 129%), respectively.

*Significantly different from Vol; Significantly different from Stim; **Significantly different from Vol at t1; †Significantly different from Vol+Stim at t1; **Significantly different from Vol at t2; ‡Significantly different from Vol + Stim; all at p <0.05.

EMG, electromyogram; HM, medial hamstring; SEM, standard error of mean; TA, tibialis anterior; VL, vastus lateralis.

Source: Adapted from Gerasimenko YP, Lu DC, Modaber M, et al. Noninvasive reactivation of motor descending control after paralysis. *J Neurotrauma.* 2015;32(24):1968–1980. doi:10.1089/neu.2015.4008.

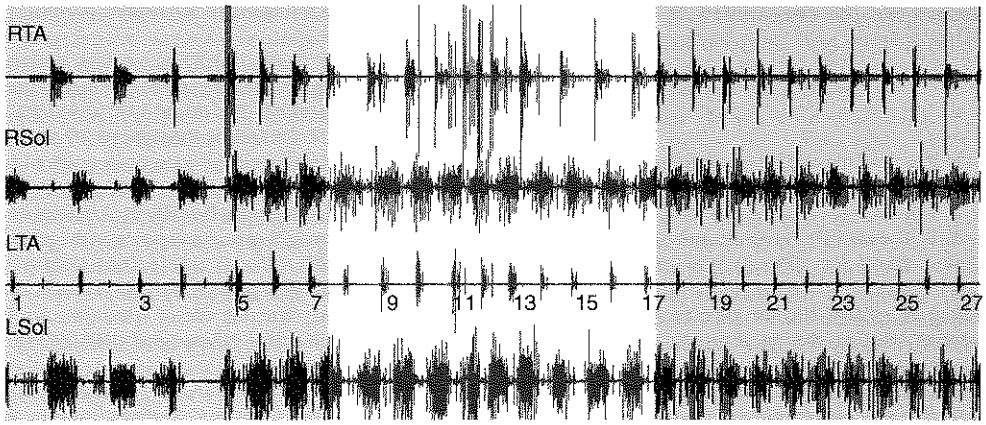

FIGURE 54.10 Representative EMG recordings from the right (R) and left (L) soleus (Sol) and TA muscles from a spinal rat supported in a harness and stepping bipedally on a treadmill at 13.5 cm/s under the influence of ES (40 Hz between L2 and S1). The rat begins to void at the beginning of the right block; however, the pattern of stepping changes several seconds (middle block) prior to voiding. Left block, normal stepping. Note the step numbers are marked by the numbers.

L, left; R, right; Sol, soleus; TA, tibialis anterior.

Source: Adapted from Gad PN, Roy RR, Zhong H, et al. Neuromodulation of the neural circuits controlling the lower urinary tract. *Exp Neurol.* 2016;285(Pt B):182–189.

was generating both stepping and voiding. Since some portion of the spinal networks controlling stepping and voiding seems to be shared, it might be expected that the effect of the electrical neuromodulation on spinal evoked responses would be evident during the transition from stepping to voiding phases (Figure 54.10). It is interesting to note that the patterns of evoked responses in the short, middle, and long latency responses during normal stepping resemble those in rats that have completely recovered their stepping abilities, whereas the evoked potentials during voiding resemble those in rats stepping prior to any step training.

CONCLUSIONS

This chapter summarizes the evolution of a new generation of clinical concepts applicable to rehabilitative strategies to improve spinal motor output that has relevance to standing, posture, walking, spasticity, and bladder function after an SCI. These concepts are based on data derived from extensive animal experimentation, mostly over the last several decades. One key concept is that a high level of processing of complex proprioceptive input occurs in the spinal cord, including in humans. The spinal cord is not simply a relay station for transmitting information to and from supraspinal centers nor is its function designed to only generate "reflex" responses when there are unexpected situations that triggers a corrective responses. It is an integrated component of networks of neurons continually and steadily making "detailed" decisions in real time from extremely complex inputs.

A second concept of fundamental importance is that although many elements of coordinated control can be derived from the brain, we now know that most of the details associated with the neural control of standing and stepping can be processed within the spinal circuitry.

A third concept is that the level of motor function that emerges after an SCI is defined in large part by use-dependent mechanisms. Although some functional and anatomical reorganization will occur spontaneously, the efficacy of the neural pathways that generate locomotion are use-dependent. Through these use-dependent mechanisms, there may be an unrecognized capacity within the spinal cord to functionally "rewire" itself (i.e., the spinal cord is highly plastic).

Fourth, it is feasible to modulate the "physiologic state" of the spinal cord via training, epidural or transcutaneous spinal cord stimulation, and with pharmacologic agents to "enable," as opposed to directly impose, the spinal cord to execute weight-bearing stepping, standing, and a range of other movements.

Finally, the spinal cord is smart. Our understanding of the concepts of spinal "smartness," however, remains rudimentary. We are only beginning to formulate the best strategies to utilize motor training paradigms (i.e., how much time per day to train, how often to train, how specific the training tasks should be, and so forth). We also must learn to individualize the strategies and learn how to change them with and according to the needs of the individual. The resolution of some of these factors details can have a significant impact on the success of a program for rehabilitating standing, stepping, and postural control after an SCI.

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AUTHOR DISCLOSURE STATEMENT

V.R.E., Y.P.G., and P.G., and researchers on the study team hold shareholder interest in NeuroRecovery Technologies and hold certain inventorship rights on intellectual property

licensed by The Regents of the University of California to NeuroRecovery Technologies and its subsidiaries.

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