Central Pattern Generation of Locomotion: A Review of the Evidence

Neural networks in the spinal cord, referred to as “central pattern generators” (CPGs), are capable of producing rhythmic movements, such as swimming, walking, and hopping, even when isolated from the brain and sensory inputs. This article reviews the evidence for CPGs governing locomotion and addresses other factors, including supraspinal, sensory, and neuromodulatory influences, that interact with CPGs to shape the final motor output. Supraspinal inputs play a major role not only in initiating locomotion but also in adapting the locomotor pattern to environmental and motivational conditions. Sensory afferents involved in muscle and cutaneous reflexes have important regulatory functions in preserving balance and ensuring stable phase transitions in the locomotor cycle. Neurmodulators evoke changes in cellular and synaptic properties of CPG neurons, conferring flexibility to CPG circuits. Briefly addressed is the interaction of CPG networks to produce intersegmental coordination for locomotion. Evidence for CPGs in humans is reviewed, and although a comprehensive clinical review is not an objective, examples are provided of animal and human studies that apply knowledge of CPG mechanisms to improve locomotion. The final section deals with future directions in CPG research.


Key Words: Central pattern generator, Locomotion, Movement sciences, Rehabilitation, Spinal cord.

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Walking is a complicated motor act requiring the coordination of trunk and limb muscles, crossing many joints. How the nervous system manages to accomplish this complex task has intrigued investigators for years. The first suggestion that the spinal cord may contain the basic neural circuitry needed to generate walking motions came from studies near the beginning of the last century. Sherrington\(^1\) demonstrated that cats, made decerebrate by cutting the spinal cord at the level of the brain stem, could perform rudimentary stepping movements. A year later, Brown\(^2\) made similar observations, using decerebrate cats that also had undergone transection of the spinal cord at T12 and deafferentation by cutting the afferent nerves from the hind-limb muscles. Brown concluded that the “mechanism confined to the lumbar part of the spinal cord is therefore sufficient to determine in the hindlimbs an act of progression.”\(^2\)(p308) Despite this corroborating evidence, decades passed before concerted efforts were made to uncover the mechanisms involved in such phenomena.

Today, the existence of networks of nerve cells producing specific, rhythmic movements, without conscious effort and without the aid of peripheral afferent feedback, is indisputable for a large number of vertebrates. These specialized neural circuits are referred to as “neural oscillators” or “central pattern generators” (CPGs). Research on CPGs has flourished, in part, because the repetitive, stereotypical nature of the resulting movements is conducive to attaining stable, reliable data. In addition, the rhythmic activities generated by the circuits are often involved in control of vital functions. Circuits for breathing, chewing, and swallowing are located in the brain stem,\(^3\)\(^4\) whereas those for locomotive functions are contained in the spinal cord.\(^5\)

This review focuses on the spinal cord generators (spinal CPGs) of locomotion.

Evidence for spinal circuits has been obtained from a host of invertebrate and vertebrate preparations. Although there is always the question of whether data obtained from one species of animals can be applied to other species, the general neural organization of CPGs subserving locomotion appears to be quite similar in all the species studied.\(^6\) This is indeed surprising considering the very dissimilar modes of locomotion, from swimming, to walking, running, hopping, and flying. Even the coordination patterns of the upper and lower extremities in human bipedal locomotion have features in common with those of quadrupedal locomotion.\(^7\)

Evidence of pattern generation derived from humans is, by necessity, indirect, and at present, quite rudimentary.\(^8\)\(^9\) Although studies of animals often involve the use of intrusive, unnatural conditions, the benefits of using simpler animal models are the absence of complexity (relative to the human) and easier access and manipulation of the circuits. Although studies of invertebrates have contributed substantial insights into the mechanisms of CPGs, this review is limited to studies using vertebrate models.

The fact that investigators have been able to obtain rhythmic movements in preparations devoid of supraspinal inputs\(^10\)\(^–\)\(^12\) and sensory inputs\(^13\)\(^–\)\(^15\) should not be interpreted as meaning that such inputs are not important in pattern generation by animals with intact spinal systems. Indeed, the CPG is only part of the motor control system. Furthermore, it has not been proven that CPG activity is essential to functional movement. The interplay between central and sensory influences is critical in the production of adaptive behaviors, as will be addressed in this review of the evidence of locomotor CPGs.

Evidence of Locomotor CPGs

In the mid-1980s, a critical paradigm shift occurred in the field of motor control—a shift away from the belief that reflexes were the bases for motor behavior and toward the belief of the motor program as the fundamental substrate underlying motor behavior. Baev and Shimansky quoted Pavlov, who earlier in the last century wrote that “the enormous part of higher nervous activity is largely, if not wholly, explained by the physiologist on the basis of the conditioned reflex.”\(^16\)(p47) Subsequent experiments, however, demonstrated that voluntary motor tasks, such as reaching and grasping, and more automatic rhythmic movements, including walking, and swimming, could still be performed following deafferentation.\(^13\)\(^–\)\(^15\) Out of such investigations emerged the concept of the motor program, defined by Marsden and colleagues as “a set of muscle commands which are structured before a movement begins and which can be

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This article was submitted May 5, 2000, and was accepted September 12, 2001.
sent to the muscle with the correct timing so that the entire sequence is carried out in the absence of peripheral feedback.15(p256) Emergence of the notion of the motor program as the basic unit of motor control renewed interest in the concept of spinal CPGs.

Research on animals that have undergone transection of the spinal cord has revealed that the spinal cord, when excited by cutaneous stimulation, limb movements, or pharmacological agents, can produce stereotyped rhythmic movements. Following complete transection of the thoracic spine in adult cats, alternating and coordinated movements of the hind limbs can be achieved on a treadmill.17,18 These movements persist even if afferent input from the involved limbs has been abolished.19 Moreover, following application of paralytic agents (eg, curare) to block receptors at the neuromuscular junction—eliminating movement and therefore feedback of movement—locomotor patterns can still be recorded in ventral roots or motoneurons.20 Because these rhythmical patterns occur in the absence of any movements, such neural activity is referred to as "fictive locomotion." Studies of the combined use of deafferentation and paralysis have demonstrated that sensory input is not necessary in the generation of these stereotyped locomotor patterns.20 These findings do not imply, however, that, under normal conditions, sensory feedback is unimportant for functional locomotion.

Isolated nervous system preparations have also yielded evidence of autonomous functioning of the spinal cord in generating locomotor patterns (Fig. 1A).21 Using a neonatal rat spinal cord–hind-limb preparation, Cazalets et al22 observed that bath application of neuroactive substances (eg, serotonin [5-HT] and N-methyl-D-aspartate [NMDA]) used to induce locomotor-like rhythmicity triggered fictive locomotor patterns in the recordings from the lumbar ventral roots (Fig. 1B). Magnuson and Trinder23 used a similar preparation to demonstrate that electrical stimulation of a descending locomotor pathway in the low cervical region caused alternating activity of ipsilateral and contralateral lumbar ventral roots in a pattern consistent with locomotion.

Little is known about the structural organization of CPGs in higher vertebrates. Many researchers have relied on simpler vertebrate models, particularly the lamprey eel, to explain how an ensemble of spinal neural elements can elicit rhythmic motor patterns in the absence of external feedback (see recent reviews24,25). Other investigators26,27 have turned to computer modeling of cellular properties and interactions in different neuronal systems to explore how motor circuits produce rhythmic outputs. The "half center" hypothesis proposes that rhythmic motor activity is generated by reciprocal inhibition between 2 pools of interneurons located on each side of the spinal cord—an extensor half center activating extensor motoneurons and a flexor half center exciting flexor motoneurons.28 Answers to the question of where in the spinal cord CPGs are located remain somewhat elusive. It appears that the CPG networks controlling hind-limb movements in quadrupedal vertebrates are distributed throughout the hind-limb enlargement and the lower thoracic cord, but their location in the transverse plane seems to be species-specific.29 Dickinson30 advocated that CPGs should be defined by the
behaviors that they produce rather than by their anatomical location.

Do CPGs exist in humans? The “best guess” at this point is cautious affirmation. The evidence that exists is necessarily indirect. For example, Calancie et al provided support that they described as “the first well-defined example of a central rhythm generator for stepping in the adult human.” Their claim may have been overstated in that it was based on a study of a single person with a chronic incomplete injury to the cervical spinal cord. Involuntary rhythmic movements of his lower extremities were triggered when he was positioned supine with the hips in extension and were abolished by flexing the hips, by standing, and while sleeping in the supine position. More recently, Dimitrijevic and colleagues elicited patterned, locomotor-like activity in subjects with long-standing complete spinal cord injury (SCI) by applying epidural electrical stimulation to the L2 segment. Although these observations offer some evidence that an involuntary locomotor pattern can be generated in humans, they fail to isolate the neural circuitry responsible for the movements. Further testimony to the existence of locomotor CPGs in humans comes from studies of gait retraining following SCI, a topic addressed later in this review.

**Supraspinal Influences on Locomotor CPGs**

Prior to the development of the notion of motor programming, the relationship between voluntary and automatic movements was considered by many researchers to be of a dichotomous nature. Simply stated, movements were either voluntary or automatic. It is now clear that motor behavior is on a continuum—the same motor programs may be involved in behaviors that have been traditionally considered as either voluntary or automatic. What determines where on the continuum the behavior occurs depends, at least in part, on the context in which it occurs. What is volitional in a voluntary movement is its purpose. To some extent, the context determines the mix of supraspinal and spinal influences involved in generating the movement.

Grillner cited a 1966 experiment in which Russian neurophysiologists demonstrated that decerebrate cats could walk when subjected to repetitive electrical stimulation of the brain stem. Moreover, the speed and mode of locomotion (ie, walking, trotting, galloping) were dependent on the strength of stimulation. Bjursten and colleagues reported that the locomotion of cats that had the cerebral cortex removed as neonates was purposeful and similar in pattern to that of cats with intact cortices. Other studies using decerebrate animals have produced similar findings.

Although the interaction of supraspinal influences and CPGs remains unclear, 2 points seem to be generally agreed upon. The first is that supraspinal control of the spinal locomotor CPGs appears to be similar for all classes of vertebrates. From lampreys to primates, nuclei in the mesencephalon, referred to as the “mesencephalic locomotor region” (MLR), initiate locomotion through activation of lower brain-stem reticulospinal neurons. In the cat, 2 distinct descending tracts are involved—the medial longitudinal fasciculus (MLF), with cells originating in the medial pontomedullary reticular formation, and the lateral vestibulospinal tract, with cells originating in the lateral vestibular (Deiters’) nucleus. Transmission to flexor motoneurons is facilitated during the flexion phase of stepping, and transmission to extensor motoneurons is facilitated during the extensor phase of MLR-evoked fictive stepping. Gossard et al suggested, but did not demonstrate, that this modulation may involve premotoneuronal convergence of locomotor CPG and descending inputs onto common interneurons, such that the descending input “shapes” the output patterns generated by the CPG.

The second point is that the supraspinal-CPG interaction is far more complex than previously thought. Computer modeling suggests that the feedforward input from reticulospinal neurons can have variable and unpredictable effects on spinal CPGs. Feedback via spinoreticular neurons and inputs from other regions of the brain appear to be necessary to stabilize the locomotor rhythm. Grillner and Matsushima noted that the brain stem, as a site of convergence of several inputs, appears to provide a locomotion-related gating function involving spinoreticular input from the CPGs together with other forms of input, such as from the visual and vestibular systems. As a consequence, the animal’s behavior is more responsive to its environmental context.

Orlovsky identified 5 functions of supraspinal areas in the control of locomotion: activating spinal locomotor CPGs, controlling the intensity of CPG operation, maintaining equilibrium during locomotion, adapting limb movement to external conditions, and coordinating locomotion with other motor acts. Spinal CPGs are left to generate the complex patterns of muscle activity required for locomotion. Among the main supraspinal centers involved are the sensorimotor cortex, the cerebellum, and the basal ganglia. After sustaining lesions of the sensorimotor cortex or the corticospinal tract, cats can perform tasks such as walking and running at varying speeds uphill and downhill reasonably well. However, with mobility tasks of increasing complexity, the need for an intact sensorimotor cortex becomes apparent. For example, Figure 2 shows the activity recorded from a pyramidal tract neuron in the motor cortex during locomotion over a level surface (“control”) or over a
The basal ganglia are now considered as integral parts of larger, distinct circuits involving the cerebral cortex and thalamus, and they have been implicated in a wide variety of motor functions, including the planning, initiation, execution, and termination of motor programs as well as motor learning. Both the cerebellum and basal ganglia seem to play an important role in timing of sequential muscle activation, with the basal ganglia operating on a longer time scale. Purposeful and successful movement through the environment requires the cooperation of spinal mechanisms and supraspinal centers.

Returning to the 5 functions identified by Orlovsky, it would appear that innumerable parallel processes are in place within supraspinal centers to facilitate these functions.

**Influence of Sensory Afferents on Locomotor CPGs**

Results of studies involving deafferentation, nervous system isolation, and paralysis unequivocally support the notion that the nervous system is capable of generating rhythmic motor output in the absence of peripheral feedback. However, the resulting movements, although remarkably similar, are clearly not identical to those in animals with intact nervous systems. Brown commented, with respect to proprioceptive input, “There can be no question of its importance nor its suitability to augment the central mechanisms. . . . Its part must be regulative not causative.” Today, this notion still holds—sensory feedback is an integral part of the overall motor control system and is critical in modifying CPG-generated motor programs in order to facilitate constant adaptations to the environment. Without question, afferent input plays an important role in stabilizing the resulting motor behaviors. Many experiments have shown that sensory feedback can drive or terminate a rhythmic behavior without being necessary for the normal expression of the behavior. Thus, afferent input is usually regarded as important but extrinsic to CPG functioning. The influence of such input on the final motor output continues to be delineated vigorously.

Pearson identified 3 potential roles for afferent feedback in the production of rhythmic movements, and all 3 roles involve adapting movement to changes in the internal and external environments. The first role is that of reinforcing CPG activities, particularly those involving load-bearing muscles, such as the hind-limb extensor muscles during the stance phase of gait. The second role is a timing function whereby the sensory feedback provides information to ensure that the motor output is appropriate for the biomechanical state of the moving body part in terms of position, direction of movement, and force. The third role is that of facilitating phase transitions in rhythmic movements, purportedly to ensure that a certain phase of the movement is not initiated until the appropriate biomechanical state of the moving part has been achieved.
Low-threshold cutaneous receptors exert an excitatory influence on locomotion in the cat model in a phase-dependent manner, thus illustrating the second role of sensory afferents identified by Pearson—

that of a timing function. For example, stimulation of the cutaneous nerve supplying the dorsum of the foot typically enhances extensor activity during the stance phase and flexor activity during the swing phase during fictive locomotion of decerebrate-paralyzed cats or decerebrate cats with transected spinal cords. Use of animals with transected spinal cords in the study by LaBella et al ruled out a substantial supraspinal contribution to this reflex reversal. Convergence of control information from locomotor CPGs onto segmental interneurons in the oligosynaptic pathway from cutaneous receptors to alpha motoneurons has been postulated to be the source of the reflex modulation observed in the cat forelimb and cat hind limb during fictive locomotion.

The issue of phase-dependent modulation of muscle stretch receptor inputs during human locomotion has been reviewed extensively. Phasic modulation of Ia input has been demonstrated by changes in magnitude of stretch reflexes and of H-reflexes during the stance phase and flexor activity during the swing phase during fictive locomotion of decerebrate-paralyzed cats or decerebrate cats with transected spinal cords. Use of animals with transected spinal cords in the study by LaBella et al ruled out a substantial supraspinal contribution to this reflex reversal. Convergence of control information from locomotor CPGs onto segmental interneurons in the oligosynaptic pathway from cutaneous receptors to alpha motoneurons has been postulated to be the source of the reflex modulation observed in the cat forelimb and cat hind limb during fictive locomotion.

Pearson’s third role of sensory feedback, that of triggering phase transitions in alternating movements, is illustrated in the control of the cat locomotion, where sensory signals switch the CPG motor program from stance to swing near the end of the stance phase. Experiments involving treadmill walking have demonstrated that the rate of stepping adapts to the speed of

Figure 3.

the treadmill in decerebrate cats, cats with transected spinal cords, and cats with intact neurological systems. The phase shift of terminating extension and initiating flexion is purported to involve 2 mechanisms: hip extension and unloading of hind-limb extensor muscles, each being subserved by a different type of afferent input. Hip extension activates the afferents arising from the muscle spindles of the elongated hip flexor muscles, thereby triggering the monosynaptic stretch reflex, which initiates a flexor burst near the end of the stance phase. The critical role of hip joint afferents in the control of locomotion has been reinforced by evidence of sensory-evoked entrainment of the locomotor pattern in decerebrate cats during fictive locomotion.

A revised notion of the influence of Ib afferent feedback to the locomotor CPGs is beginning to emerge. Stimulation of Ib afferents from the Golgi tendon organs (GTOs) of ankle and knee extensors during fictive locomotion in cats with acutely transected spinal cords evoked excitation of extensor motoneurons, rather than the anticipated Ib autogenic inhibition (Fig. 4A). The authors cautioned that findings attained used dopa-induced fictive locomotion may not reflect the normal function of proprioceptive feedback. However, in subsequent studies using MLR-activated fictive locomotion and spontaneously evoked locomotion of decerebrate cats, similar results were found. Guertin and colleagues concluded that both Ia and Ib afferents from extensor muscles help to shape the amplitude, duration, and timing of ipsilateral extensor activity. In an attempt to explain the unexpected findings regarding the effects of Ib afferents, Pearson hypothesized that, in addition to the disynaptic inhibitory pathway from group Ib afferents to extensor motoneurons, there may be 2 additional pathways that open only during locomotor activity—a disynaptic excitatory pathway from group Ib afferents to extensor motoneurons and an oligosynaptic pathway from group Ib afferents to extensor motoneurons via the CPG extensor “half center” (Fig. 4B). Rossignol and Dubuc advocated that with this example of possible “reflex reversal” from a static to a dynamic condition, classic notions of reflex actions should be revisited with regard to rhythmic motor behaviors.

Findings from a preliminary study involving humans reinforce the hypothesized involvement of load-detecting receptors (GTOs) in the facilitation of stepping. Harkema and colleagues found that in 2 subjects without neurological pathology and 4 subjects with SCIs, modulation of the EMG activity of lower-extremity muscles was more closely associated with the degree of lower-extremity loading than with either the extent or velocity of muscle-tendon length changes during assisted treadmill walking. In addition, the EMG amplitude within a step was highly dependent on the phase of the step cycle. Although the authors suggested that their findings support the existence of spinal cord CPGs in humans, the sample size yields insufficient power and the results are too variable to be convincing.

An exciting new area of research in neuroplasticity involves the possibility of plastic changes in reflex pathways at the level of the spinal cord. Whelan and Pearson demonstrated in the decerebrate cat that when the nerve to the lateral gastrocnemius-soleus muscle is cut, reflex activity from the synergistic medial gastrocnemius muscle is heightened. Moreover, this compensatory strategy to control the timing of the step cycle persists after spinal cord transection at the T12 level.

From the evidence to date, it seems likely that sensory inputs—particularly limb loading and proprioception—provide the information required by the CPG circuitry to...
generate functional and adaptive locomotion. Various afferent pathways (e.g., Ia, Ib, II, and cutaneous afferents) modify the neuronal composition of the active CPG circuits and synaptic connections within the circuits, thereby “shaping” the final motor program producing rhythmic movements.3

Influence of Neuromodulators on CPGs
There is a growing recognition that neuromodulators can modify the functional properties of the CPGs.22,63,64 The modulating effects of supraspinal input, sensory afferents, and, now, neuromodulators make it abundantly clear that CPGs do not produce immutable, stereotyped motor patterns but rather flexible, adaptive patterns that are sculpted by plastic mechanisms. Neuromodulators are neurotransmitter-like substances, delivered by the bloodstream or more rapidly via synaptic terminals, that enhance or diminish the effect of the primary neurotransmitters with which they coexist in nerve terminals. These substances alter the functional properties of neuronal circuits by facilitating, depressing, or initiating motor activity as well as by modifying the cellular and synaptic characteristics of neurons. Within CPG networks, neuromodulators are classified as intrinsic or extrinsic, the former being an integral part of the CPG and the latter modulating CPG activity from other areas of the nervous system.64

Despite the seemingly ubiquitous presence of neuromodulators in vertebrate motor systems, the function of specific modulators has been established mainly in lampreys and neonatal rats with transected spinal cords. Neurotransmitters (e.g., glutamate, y-aminobutyric acid [GABA], glycine), as well as the neuromodulators (e.g., serotonin [5-HT], dopamine), have been shown to influence locomotor CPG behavior.22,65 In addition, peptides (e.g., neurotensin; somatostatin; tachykinins, including substance P) exert neuromodulatory effects on the locomotor CPGs, although their actions are not yet well defined.65,66

Coordination Among Locomotor CPGs
Central pattern generators are not isolated entities but are interconnected in terms of circuitry and overlap in the behaviors that they generate. Interaction among CPGs has been considered mainly from the theoretical perspective. Two hypotheses have been put forth that are not necessarily mutually exclusive in that different mechanisms may be used by different animals depending on the complexity of the animals’ movement repertoire or by the same animal for different behaviors. The “shared CPGs” hypothesis postulated by Grillner 32 to explain lamprey movement may also apply to limbed vertebrates. The locomotor network may consist of distinct spinal CPGs, with descending pathways activating individual CPGs for selective control of joints or muscle groups. Coordinated movement within a limb could be achieved through phase-dependent interactions of different CPGs controlling that limb (e.g., between hip and knee CPGs). Motor learning may involve learning which combination and sequence of CPGs are involved in producing the appropriate motor output.

The “shared interneurons” hypothesis depicts CPG networks as systems wherein complex movements are configured from pools of multipotent interneurons.30 Dickinson 30 suggested that pattern generators should be defined by the behaviors they produce rather than by anatomical boundaries. Extensive “sculpting” of CPG networks by using different combinations of basic cellular and synaptic processes creates a variety of alternative functional circuits, each with the capacity to generate a distinct motor pattern within a family of function-related behaviors.5,67 For example, analysis of rhythmic activities in cats (e.g., locomotion, scratching) suggests that many common interneurons are shared in the generation of these motor tasks.16 Similarly, commonalities in the kinematic analysis of hatching, walking, and swimming in chicks suggest that these distinct, but related, motor behaviors may result from reconfigurations of interneurons within a common CPG pool.88 Influences on CPGs that have been discussed (e.g., sensory afferents, supraspinal influences, neuromodulators) have been implicated in “circuit-switching” mechanisms4;6; however, details of the mechanisms are not yet known.

Little evidence exists concerning coordination between segments or limbs in human gait. Alterations in coupling patterns between upper and lower extremities associated with changes in walking speed implicate interaction among CPGs.7 Using a split-belt treadmill protocol to study interlimb coordination, Dietz and colleagues8 found that increasing the ipsilateral speed while maintaining the contralateral speed was associated with increases in ipsilateral gastrocnemius muscle and contralateral tibialis anterior muscle EMG activity. These findings are consistent with a model of flexible coupling of separate locomotor centers controlling each limb. In a subsequent study of split-belt locomotion, the researchers found adaptation to a difference in belt speeds within 12 to 15 strides, and after a short interval of walking with a common belt speed, readaptation to different belt speeds occurred within 1 to 3 strides.69 However, this motor learning effect was not transferred to the other side when the fast and slow sides were reversed. The inference was that for “CPG learning” to occur, interaction between side-specific proprioceptors and spinal interneuronal circuits is necessary.

Locomotor Retraining Studies in Animals
The possibility of using CPG neuronal circuits to restore locomotor function after injury is an issue receiving
considerable attention. Initial work with animals in this area and more recent clinical trials involving humans suggest that new rehabilitative strategies purported to exploit CPG circuits may enhance recovery of mobility. At this point, most strategies are confined to the experimental arena, but the more promising ones are likely to become mainstream approaches in the near future.

Barbeau and Rossignol\(^\text{18}\) reported that although 5 adult cats with transection of the spinal cord at the T13 level initially demonstrated a poorly organized hind-limb stepping pattern during treadmill walking with tail support, they demonstrated a “near-normal” pattern after 3 to 4 weeks of daily treadmill training. Furthermore, by the end of the trial, the cats were able to adjust the locomotor cycle to adapt to varying treadmill speeds. This study, as well as other studies conducted during the same period,\(^\text{70,71}\) countered the prevailing doctrine that an animal will recover more completely from a neurological injury sustained as a neonate than as an adult.

In the study by Barbeau and Rossignol,\(^\text{18}\) the hind limbs of the cats with spinal cord transection were too weak in the first post-surgical week to make early treadmill training efficacious. The same investigative team later attempted to facilitate more effective early training in a single cat by administering intraperitoneal injections of a noradrenergic drug (clonidine) each day from the second day to the ninth day after transection of the spinal cord to activate locomotor CPGs.\(^\text{72}\) After each injection, the cat was trained on the treadmill with a progressive increase in hind-limb weight bearing (Fig. 5A). Clonidine appeared to enhance the training effect in that the resulting locomotor pattern was similar to that achieved after 3 to 4 weeks of training in the previous study (Figs. 5B and 5C). In addition, the improved pattern continued without further clonidine injections. Similar results were obtained recently on 5 cats with transection of the spinal cord at the T13 level that were subjected to the same training protocol used by Barbeau et al\(^\text{72}\) but to a higher dose of clonidine.\(^\text{73}\) Unfortunately, the protocol did not include cats that were similarly trained but without clonidine injections, and an analysis of overground walking was not conducted.

An extension of pharmacological enhancement of locomotor CPG activity following SCI has been experimentation with neural tissue transplantation. Injections containing embryonic neurons from noradrenergic sites in the locus ceruleus or from serotonergic sites in the brain-stem raphe were administered into T12–13 segments of rats with transection of the spinal cord at T8–9.\(^\text{74}\) By approximately 6 weeks after transplantation, reciprocal activation of tibialis anterior and gastrocnemius muscles was observed, which was facilitated by administration of zimelidine, a serotonin reuptake blocker. Postmortem immunohistochemical studies revealed monoaminergic reinnervation of the lumbar enlargement. Control rats with transected spinal cords exhibited coactivation of ankle extensors and flexors with little locomotor activity, and they were totally devoid of immunoreactivity for noradrenaline and serotonin. The researchers intentionally limited analysis of treadmill locomotion to avoid a training effect. A logical next step would be to investigate the combined effect of transplantation and training.

![Figure 5.](image)
Use of treadmill training to enhance recovery of walking in animals with transected spinal cords implies some use-dependent plasticity in spinal pathways involved in locomotor generation. Few studies have demonstrated functional plasticity of the spinal cord after changes in the supraspinal or peripheral inputs. One such study involved superimposed spinal cord transection in cats that had undergone previous unilateral neurectomy of the ankle flexor nerves. Following spinal cord transection, the cats retained an asymmetric gait pattern with the compensatory strategy of knee hyperflexion on the neurectomized side. Another cat that underwent spinal cord transection first and then neurectomy did not exhibit this compensatory pattern. These findings intimate that plastic changes may have taken place in the spinal circuitry to maintain locomotion following the peripheral nerve lesion.

Edgerton and colleagues provided evidence that they interpreted as supportive of the notion that training produces functional changes or “motor learning” in the spinal motor-generating circuitry. They reported that adult cats with transection of the spinal cord at the T13 level that were trained to stand on their hind limbs had difficulty stepping and that other cats with transection of the spinal cord at the T13 level that were trained to step had difficulty maintaining a standing posture. The researchers argued that the specificity of the training effect on recovery of mobility was neural in origin as opposed to muscular in origin because similar muscular activity was involved in both tasks. They also noted that although both groups had 30-minute training sessions daily during the interval from 1 month to 6 months following transection, performance peaked between 2 months to 4 months after transection. A common persistent abnormality in the “stepping” group was abnormal coactivation of hind-limb flexor and extensor muscles.

**Locomotor Retraining Studies in Humans**

A direct extension of findings derived from locomotor recovery studies involving animals to humans is problematic. Although the pattern of infant stepping resembles that of tetrapods and other bipeds, the pattern of mature human locomotion is unique. Forsberg identified determinants of human plantigrade gait such as heelstrike at initial contact, a loading response in early stance, pelvic-trunk rotations, and asynchronized out-of-phase activity of lower-extremity extensor and flexor muscles. Forsberg et al. later postulated that maturation of human gait may involve reorganization in the spinal CPG circuitry and more extensive supraspinal dependency in the regulation of locomotion than is found in lower vertebrates. Thus, the potential to exploit or manipulate CPGs to expedite locomotor recovery in humans may be much more difficult than it appears to be in other animals. The premise that human gait is distinct from gait of all other vertebrates is based on sound evidence.

Another consideration precluding a literal extrapolation of findings from animal studies to humans is the greater inability of humans to maintain an upright posture following SCI. Even if neuronal activity were to be restored at the spinal level, the usefulness of it may be limited by the loss of equilibrium control. Nevertheless, studies of locomotor retraining in humans with impairment of the central nervous system have yielded some positive results (see review by Barbeau et al.). Visintin and Barbeau reported that in 7 people with incomplete SCI, treadmill walking with 40% of their body weight supported using an overhead frame had an immediate normalizing effect on both kinematic and kinetic aspects of the gait pattern. The authors concluded that the use of body weight support (BWS) could be an important factor in retraining locomotor abilities in people with SCI. They proposed that the mechanism involved is a decrease in the load on the extensor muscles, which facilitates inactivation of Ib afferents during the stance phase and earlier onset of the swing phase.

A recent single-subject study with an A-B-A design (6-week baseline measurement phase, 6-week treatment phase, 3-week remeasurement phase) was carried out using a subject with an incomplete C5–6 lesion sustained 7 months prior to the study. The training protocol involved constant use of 32% BWS during treadmill walking for 30 minutes per day, 3 days per week for 6 weeks. Small, but statistically significant (and purportedly clinically meaningful), improvements were found in walking speed and in some of the spatial variables of gait.

Wernig and Muller trained 8 people with chronic, incomplete SCIs using “Laufband locomotion” (treadmill walking) for between 6 weeks to 20 months, beginning with 40% BWS. They reported that by the end of training, EMG activity in lower-limb flexor and extensor muscles increased during locomotion but not when measured in a supine position. Overground walking without BWS improved following the intervention, offsetting a concern that training effects attained with supported treadmill walking may not carry over during walking under more natural conditions. In comparison with overground ambulation, supported treadmill walking requires fewer postural adjustments and less active plantar flexion, the latter because passive movement by the treadmill belt can augment plantar-flexor activity.

Wernig and colleagues extended their first study using a similar training protocol but with a larger sample (77 subjects with acute or chronic incomplete SCIs and 7
subjects with “functionally complete” paraplegia). Following acute rehabilitation using treadmill walking with BWS for 3 to 20 weeks, 33 (92%) of 36 subjects who initially were wheelchair-dependent could walk independently, whereas the same level of mobility was achieved in only 12 (50%) of 24 comparable subjects who underwent conventional therapy. Improvements in the former group were not accompanied by alterations in muscle force. However, the group assignment was not randomized, and the length of intervention was not consistent. None of the subjects with complete paraplegia improved with Laufband therapy.

In the same year, Dietz et al.84 reported findings of another BWS-treadmill study involving 10 subjects with complete paraplegia and 3 subjects with paraparesis. Important details such as the chronicity of the lesions and the length of the training period were omitted from the report. The 3 subjects with paraparesis benefited from training with respect to improved overground stepping and normalization of locomotor EMG activity (Fig. 6). However, in contrast to the lack of improvement in subjects with paraplegia noted by Wernig et al.,83 4 of the subjects with paraplegia demonstrated decreased coactivation of ankle dorsiflexors and plantar flexors and increased, albeit still abnormally low, gastrocnemius muscle EMG activity during stance following training with as much as 70% BWS. The authors concluded that “complex bilateral leg muscle activation combined with coordinated stepping movements is demonstrated in patients with complete paraplegia.”84(p574)

This statement, in my view, is misleading because advancement of the limbs on the treadmill could only be accomplished by the assistance of another person throughout the training period. Stewart and colleagues85 showed that assisted movements of the lower extremities during supported treadmill walking induced EMG activity because of the rhythmic passive stretches of the muscles. Furthermore, when this assistance was withdrawn, the EMG pattern also ceased. Consequently, the findings by Dietz and colleagues84 concerning subjects with complete SCIs may have been due to experimental artifact.

The use of BWS has been investigated in pathologies other than SCI. Seven patients with hemiplegia who were, on average, 6-months post-stroke participated in a crossover study of treadmill training with BWS.86 Three weeks of 30-minute daily sessions of treadmill walking was followed by 3 weeks of 45-minute daily sessions of conventional physical therapy and then another 3 weeks of treadmill training. The level of BWS was progressively decreased to 0% BWS from an initial level of 30% BWS. The term “nonambulatory” used by the authors to describe the participants was misleading, in my view, because all subjects could walk with assistance. An increase in gait speed and reduced dependence on ambulatory assistance were identified as important effects of treadmill training in comparison with conventional therapy. However, because the order of treatments was not randomized and the crossover design used cannot control for cumulative treatment effects, I believe the findings are somewhat spurious.

In a subsequent study, Hesse et al.87 compared floor walking with treadmill walking with 0%, 15%, and 30% BWS in 18 patients with chronic hemiparesis and found greater symmetry of weight-bearing during treadmill walking irrespective of the extent of BWS. They also observed reduction in both out-of-phase plantar-flexor activity and antigravity muscle activity with increasing percentages of BWS. Researchers from the same laboratory recommended, in an earlier study,88 that an upper limit of 30% BWS should be used to facilitate the gait of people with hemiparesis in order to avoid undesirable reductions in activation of antigravity lower-extremity muscles. The EMG amplitude of the lower-extremity muscles during BWS-facilitated locomotion has been shown to be closely associated with peak limb load.61 Hassid et al.89 found that limb loading of patients post-stroke while stepping was optimized with 15% BWS, intimating that unweighting of 15% of body mass provides the most effective step-related sensory feedback to the locomotor neural networks.

In the only published randomized trial of BWS-treadmill training, Visintin and colleagues90 investigated recovery...
of gait of 100 patients post-stroke. They found greater improvements in locomotor ability (ie, balance, walking, speed, endurance) in the BWS group than in the full weight-bearing group after 6 weeks of gait training and at a 3-month follow-up evaluation. For the BWS group, the amount of support was progressively reduced from an initial level of 40% BWS.

Evidence to support clinical strategies that appear to exploit locomotor CPGs is accumulating. Use of these approaches, however, cannot be fully justified until further randomized controlled trials have been conducted and the physiologic mechanisms underlying the observed improvements have been explored. Rossignol and Barbeau caution investigators: “Given the hopes generated, it is important to . . . be critical and conservative in the interpretation of results.” Unlike the situation with animals, convincing evidence that the spinal cord contains all the neural machinery needed to generate locomotion in humans with complete spinal cord transection is lacking. What remains unclear regarding improvements in mobility and EMG activity induced by supported treadmill training is the relative contribution of plastic changes in preserved pathways versus changes in the neural circuitry of spinal CPGs. It also could be argued that part of the training effect is due to strengthening of the lower-extremity muscles, although little evidence of a strengthening effect has been reported.

Future Directions
The locomotor generating capacity of the spinal cord has long been and will continue to be a fruitful subject of investigation. Hope of further success in this exciting area is contingent on advancing our understanding of CPGs through continued physiological and behavioral research. The precise identification and location of CPG interneurons; the role, be it intrinsic or extrinsic, of motoneurons in CPG activity; the interplay of sensory afferents, supraspinal influences, and neuromodulators on CPG activity and interlimb coordination; and the nature of mechanisms that seem to be prohibiting spinal locomotion in humans are issues that need to be pursued. Because of the enormous complexity of mammalian pattern generators, these pursuits will undoubtedly necessitate continued development of neural modeling techniques. At the same time, computer models should augment, rather than supplant, experimental research. There is tremendous potential for the use of computer simulations for advancing our understanding of human movement disorders. For example, Borrett and colleagues have developed a neural network model to simulate the types of movement disturbances typical of Parkinson disease.

Better understanding of locomotor CPGs is of practical importance. Locomotor CPGs may be manipulated pharmacologically or surgically to improve the quality of movement, and thus quality of life, for people with movement dysfunction. Although complete motor recovery following neurologic injury may never be realized, recent studies provide evidence, albeit limited, that guarded optimism in this domain is justified.

Existing and developing knowledge of CPG function may also lead to opportunities in the area of technology transfer. Biorobotics, a promising area of research bridging biology and robotics, has informed and has been informed by CPG research. Beer et al cited several recent advances, including 6-legged robots modeled after cockroach locomotion and humanoid robots capable of bipedal locomotion.

Concluding Remarks
The existence of spinal locomotor CPGs in animals has been established beyond reasonable doubt, but the relative importance of CPG activity in the control of human locomotion remains to be elucidated. Accumulating physiological and behavioral evidence that adaptive processes can occur within the spinal cord has challenged the dogma that the spinal cord is a relatively nonplastic, hardwired conduit for relaying supraspinal commands. It has become clear, however, that in the intact nervous system, CPGs do not operate in a vacuum but depend on the interplay of information between the brain and spinal cord, with the final motor output shaped by sensory feedback from peripheral receptors and reconfigured by neuromodulators. Further research at each level of interaction, from molecular, cellular, and intercellular to behavioral, will inform the other levels, and, one by one, the mysteries of animal and human locomotion will be solved.

References


