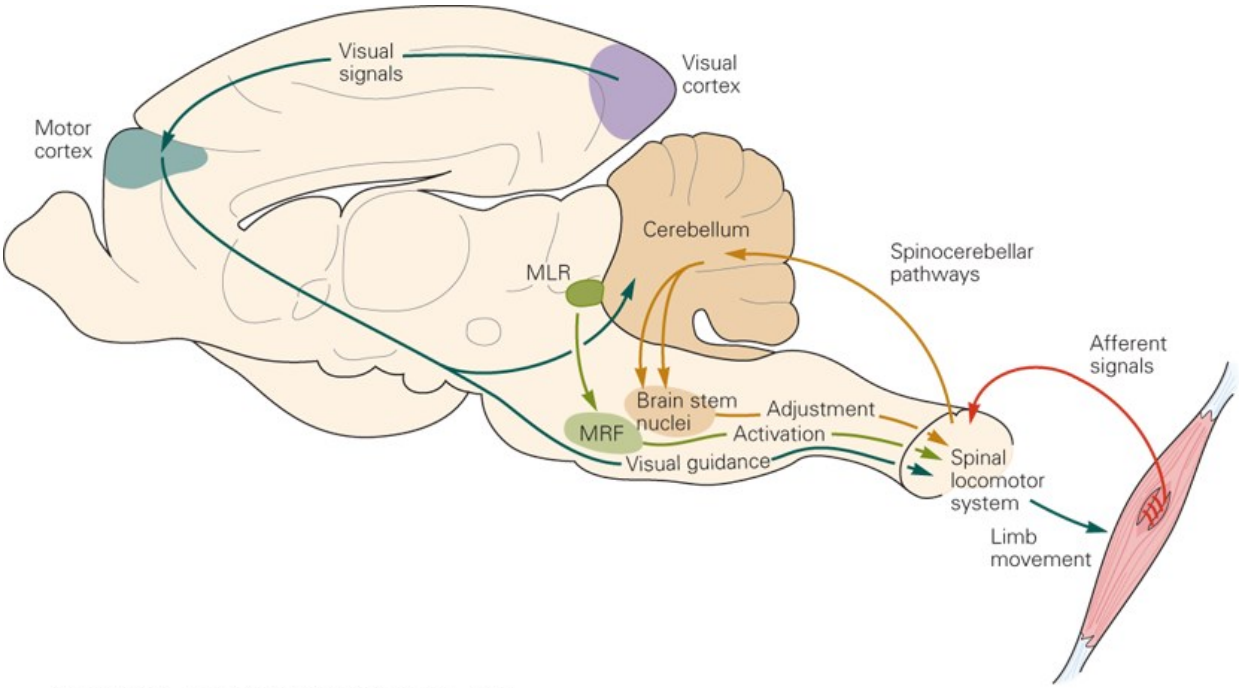
Chapter 33: Locomotion

Introduction

LOCOMOTION IS ONE OF THE MOST FUNDAMENTAL of animal behaviors and is common to all members of the animal kingdom. As one might expect of such an essential behavior, the neural mechanisms responsible for the basic alternating rhythmicity that underlies locomotion are highly conserved throughout the animal kingdom, from invertebrates to vertebrates, and from the early vertebrates to primates. However, while the basic locomotor-generating circuits have been conserved, the evolution of limbs, and then of ever more complex patterns of behavior, has resulted in the development of progressively more complex spinal and supraspinal circuits (Figure 33–1).

Figure 33–1

The locomotor system. Multiple regions of the central nervous system interact to initiate and regulate locomotion. Locomotor networks in the spinal cord—the central pattern generators (CPGs)—generate the precise timing and patterning of locomotion. Proprioceptive sensory feedback modulates the activity of the locomotor CPG. The initiation of locomotion is mediated by neurons in the mesencephalic locomotor region (**MLR**) that project to neurons in the medial reticular formation (**MRF**) in the lower brain stem, which in turn project to the spinal cord. Descending fibers from the vestibular nuclei, pontomedullary reticular formation, and the red nucleus (**brain stem nuclei**) maintain equilibrium and modulate the ongoing locomotor activity. Cortical activity from the posterior parietal cortex (not illustrated) and the motor cortex is involved in the planning and execution of visually guided locomotion, while the basal ganglia (not illustrated) and cerebellum are important for the selection and coordination of locomotor activity.



Scientists have been intrigued with the neural mechanisms of locomotion since the beginning of the 20th century, when pioneering work by Charles Sherrington and Thomas Graham Brown showed that the isolated spinal cord of the cat is able to generate the basic aspects of locomotor activity and subsequently that this capacity was intrinsic to the spinal cord. Throughout the 20th century, major advances were made in detailing both the rhythm-

and pattern-producing capacities of the spinal cord, leading ultimately to the groundbreaking concept of a central pattern generator for locomotion in the spinal cord. This single concept, more than any other, has driven research into the mechanisms underlying locomotor control since the 1970s, allowing a detailed electrophysiological examination of the neuronal mechanisms involved in the control of locomotion that is not possible for most other motor acts.

Most research throughout the 20th century on the spinal mechanisms mediating locomotion was performed on the cat, which remains an important model for studying many aspects of locomotor control. However, the complexity of the spinal circuits in mammals led to the search for simpler preparations that would allow a better understanding of the synaptic connectivity and neuronal properties responsible for the generation of locomotion. This search led to the development of the lamprey and the tadpole models (Box 33–1; Figures 33–2 and 33–3). Experiments using these species have led to a detailed understanding of the neuronal circuits responsible for generating swimming. Influential work on understanding the processes underlying locomotion has also come from other experimental models, including mouse, rat, turtle, salamander, and zebrafish.

Box 33–1 Preparations Used to Study the Neuronal Control of Locomotion

The neuronal control of locomotion is studied experimentally in diverse vertebrate species that produce swimming or over-ground locomotion, or both. The prevailing experimental models used for studying swimming are the lamprey, the tadpole, and the zebrafish; for over-ground locomotion, the cat, rat, or mouse; and for both swimming and locomotion, the turtle, salamander, and frog.

Semi-intact preparations—in which influences from parts of the brain, all supraspinal inputs, and/or afferent inputs to the spinal cord have been removed—are also commonly used in studies of the neuronal control of locomotion in vertebrates (Figure 33–2A). Finally, in vitro preparations of the spinal cord or of the brain stem and spinal cord from young animals or adult and anoxia-resistant animals are extensively used for circuit analysis (Figure 33–2C).

Intact Preparations Are Used to Study the Behavioral Output

In intact preparations, locomotion is studied either during walking over ground or on a motorized treadmill. Chronic electromyographic (EMG) recordings of limb muscles, coupled with video recordings of the movement, reveal details of the rhythm of locomotion, the pattern of muscle or joint activation, and interlimb coordination (Figure 33–2B). Such studies allow researchers to understand how normal locomotion behavior is expressed.

These behavioral studies are often combined with experimental manipulations that modify the supraspinal or afferent control of locomotion. Such experiments may use electrical stimulation or surgical ablation of circumscribed areas in the central nervous system, genetic inactivation or activation of defined populations of nerve cells, or perturbation of the afferent input to the spinal cord using genetic techniques or electrical stimulation. Finally, single-cell activity in the brain can be recorded from identified populations of neurons and correlated with specific aspects of the locomotor behavior (eg, speed, postural adjustments, gait modifications, flexor-extensor muscle activity). Cells are identified by their anatomical location, their projection pattern, transmitter content, and molecular markers.

Semi-intact Preparations Are Commonly Used to Study the Central Control of Locomotion in the Absence of Cortical Influence or Sensory Feedback

Decerebrate Preparations

In the decerebrate preparation, the brain stem is completely transected at the level of the midbrain (Figure 33–2A), disconnecting rostral brain centers, including the cortex, basal ganglia, and thalamus, from locomotor-initiating centers in the brain stem and spinal cord. These preparations allow investigation of the role of cerebellum and brain stem structures in controlling locomotion in the absence of influence from higher brain centers.

Locomotion is generally evoked by electrical stimulation of locomotor regions in the brain stem, as described in the text. To increase recording stability, the animals are often paralyzed by blocking transmission at the neuromuscular junction. When locomotion is initiated in such an immobilized preparation, often referred to as *fictive locomotion*, the motor nerves to flexors and extensor muscles discharge (recorded as an electroneurogram), but no movement takes place.

Spinal Preparations

In spinal preparations, the spinal cord is completely transected, generally at the lower thoracic level, thus isolating the spinal segments that control

the hindlimb musculature from the rest of the central nervous system (Figure 33–2A). This procedure allows investigations of the spinal locomotor circuits without any influence from supraspinal structures.

Two types of spinal preparation are used: acute spinal preparations, in which studies are performed immediately after the spinalization, and chronic spinal preparations, in which the animals are allowed to recover from the surgery and are then studied over a period of time.

In acute spinal preparations, locomotion is frequently induced chemically, either by intravenous administration of drugs that stimulate monoaminergic and/or serotonergic receptors or by local application of glutamatergic receptor agonists. These drugs increase the excitability in the spinal locomotor circuits, mimicking the locomotor-initiating drive from the brain stem. Alternatively, locomotion is induced electrically, by stimulation of the dorsal roots or dorsal columns. Acute spinal preparations are often paralyzed in order to increase recording stability from motor neurons and interneurons in the spinal cord, as well as to discriminate between central and peripheral effects.

In chronic spinal preparations, animals are studied for weeks or months after transection, often with the aim of finding better ways to improve the locomotor capability after spinal cord injury. In both young and adult cats and in young rodents, the hindlimb locomotor capability can often return following training but with no further treatment. In all animals, the locomotor capability is improved dramatically by drug treatments that activate the spinal central pattern generator. Electromyographic activity, together with behavioral measures, can be recorded before and after transection (Figure 33–2B).

In Vitro Preparations Are Used to Study Central Organization of Networks

With in vitro preparations, the spinal cord or brain stem is removed from the animal and placed in a bath that is perfused with artificial cerebrospinal fluid (rodent, lamprey, and turtle) (Figure 33–2C). Alternatively, the brain stem and spinal cord are left in situ in the animal that is paralyzed or immobilized and kept in vitro (tadpole and zebrafish) (Figure 33–2D).

In all cases, no rhythmic afferent inputs occur in the cord, and motor activity is recorded in peripheral nerves or, more often, in the ventral roots where the motor neurons have their axons leaving the spinal cord.

Locomotion is induced chemically, either by application of glutamatergic or serotonergic receptor agonists or a combination of both, or electrically by stimulating the brain stem or peripheral afferents. Rhythm and pattern generation, circuit connectivity, cellular properties of interneurons and motor neurons, and circuit neuromodulation are studied with conventional electrophysiological methods, imaging, and anatomical tracing, or with molecular genetic methods that allow manipulation and recording of identified populations of neurons.

Figure 33–2

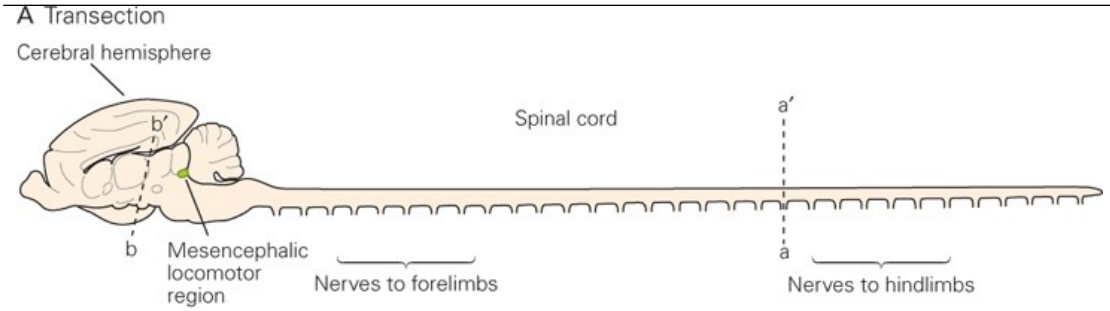
Selected animal models used to study locomotor control systems.

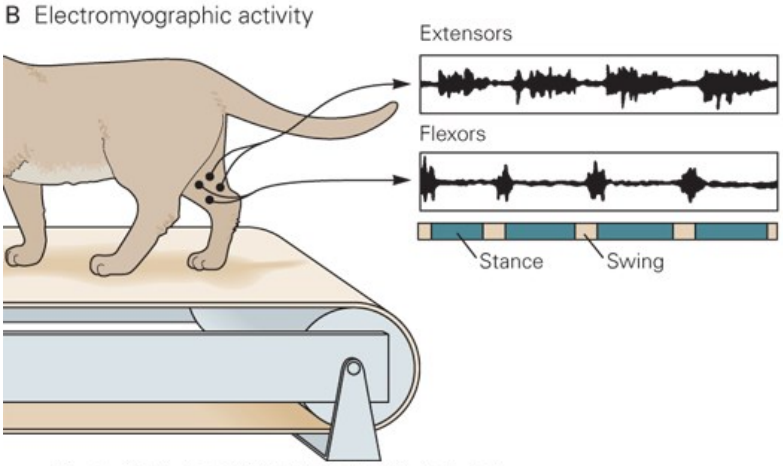
A. Schematic of the cat cerebral hemispheres, brain stem, and spinal cord showing the level of transection for spinalization (**a′-a**) and decerebration (**b′-b**). Decerebration isolates the brain stem and spinal cord from the cerebral hemispheres. Transection at a′-a isolates the lumbar spinal cord from all descending inputs.

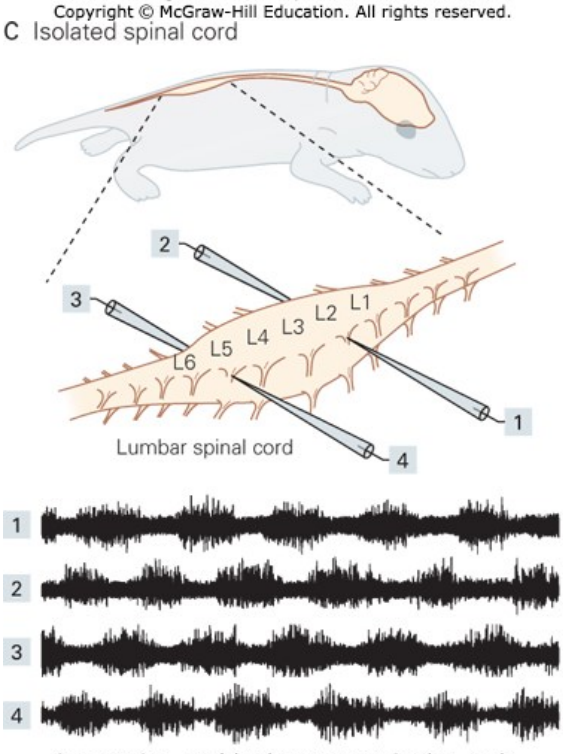
B. The electromyogram can be used to record locomotor activity during actual movement in intact, decerebrate, or spinal animals.

C. The isolated lumbar (L1–L6) spinal cord from a newborn rat or mouse. Motor activity is recorded in flexor-related L2 ventral roots and extensor-related L5 ventral roots on either side of the cord. Locomotor-like activity is induced by application of *N*-methyl-D-aspartate (NMDA) and serotonin (5-hydroxytryptamine, 5-HT) to the bathing solution. Flexor-extensor alternation is seen as out-of-phase activity between L2 and L5 ventral roots on the same side of the cord (**1** and **4**; **2** and **3**), and left–right alternations are seen as out-of-phase activity between L2–L2 and L5–L5 ventral roots on either side of the cord (**1** and **2**; **3** and **4**). (Adapted, with permission, from Kiehn et al. 1999; data from O Kiehn.)

D. In vitro tadpole preparation, in which the spinal cord remains in situ, showing ventral root recordings on the right side (**1**) and on the left side (**2** and **3**). side of the spinal cord. The swimming rhythm in the nervous system of the paralyzed animal was induced by a brief stimulation of the skin on the head. (Data from L Picton and KT Silar.)







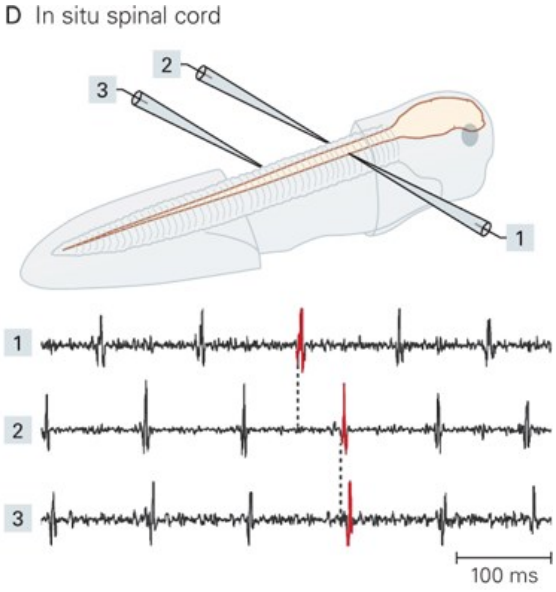
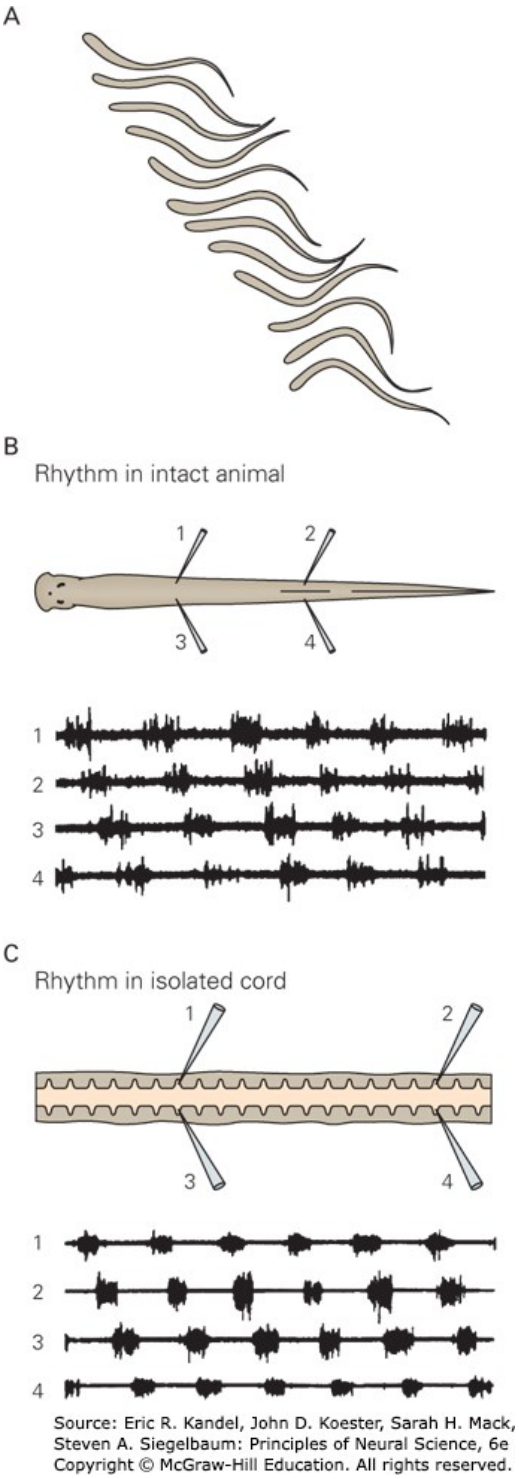


Figure 33–3

Lamprey swimming. The lamprey swims by means of a wave of muscle contractions traveling down one side of the body 180° out of phase with a similar traveling wave on the opposite side (**A**). This pattern is evident in electromyogram recordings from four locations along the animal during normal swimming (**B**). A similar pattern is recorded from four ventral roots in an isolated cord (**C**). (Data from S Grillner.)



More recently, the development of molecular-genetic techniques has provided a powerful tool to probe the spinal circuits responsible for locomotion in preparations as diverse as zebrafish and mouse. These techniques have allowed researchers to explore more thoroughly both the neuronal circuits

in the mammalian spinal cord responsible for rhythmic, alternating patterns of activity that define over-ground locomotion and those responsible for swimming.

The rhythmic pattern of activity is only one element of the complex locomotor behavior observed in most vertebrates, especially mammals, which have evolved to allow them to move quickly and elegantly. This flexibility is provided via feedback and feedforward modification of the locomotor patterns generated by spinal networks.

Feedback information from the body and limbs in the form of cutaneous and proprioceptive inputs is important for regulating aspects of the locomotor cycle, including bending of the body, stride length, and the force produced during propulsion. This information is equally critical in assuring that animals can rapidly and efficiently react to unexpected perturbations in the environment, such as when hitting a branch during walking or stepping on an unstable surface.

Feedforward information from supraspinal systems modifies activity according to the goals of the animal and the environment in which it moves. Information from defined structures in the brain stem is important for both the initiation of locomotion and for regulating general aspects of locomotor activity, including the speed of locomotion, level of muscle activity, and interlimb coupling in animals with limbs. Information from cortical structures contributes primarily to the planning and execution of locomotion in situations in which vision is used to make anticipatory modifications of gait. Finally, two structures with no direct spinal connections, the basal ganglia and the cerebellum, contribute to the selection of locomotor activity and to its coordination (Figure 33–1).

The way in which all of these structures interact and permit diverse modes of locomotion is the subject of this chapter.

Locomotion Requires the Production of a Precise and Coordinated Pattern of Muscle Activation

Locomotion requires the production of activity in many muscles that need to be coordinated in a precise rhythm and pattern. The rhythm defines the frequency of the cyclic activity, whereas the pattern defines the spatiotemporal activation of muscle groups within a cycle. In swimming animals, such as the lamprey or the tadpole, locomotion is expressed as a traveling wave of activity (Figure 33–3A) that propagates from rostral to caudal body segments during forward progression. This pattern can be recorded as an electromyogram (EMG) during locomotion in the intact animal (Figure 33–3B) and as an electroneurogram in the isolated spinal cord (Figure 33–3C). Activity in more caudal roots occurs later than that in more rostral roots, and the activity on each side of the body is reciprocal.

In limbed animals, the pattern of muscle activity is more complex and serves to support the body as well as to transport it forward. The general unit of measure of locomotion in limbed vertebrates is the *step cycle*, which is defined as the time between any two successive events (eg, foot or paw contact of a given limb). The step cycle is divided into a *swing* phase, when the foot is off the ground and being transferred forward, and a *stance* phase, when the foot is in contact with the ground and propelling the body forward. Based on measures of changes in joint angle, each of these phases can be further divided into a period of flexion (F) followed by an initial period of extension (E_1) during swing and two additional periods of extension (E_2 and E_3) during stance (Figure 33–4A; see below).

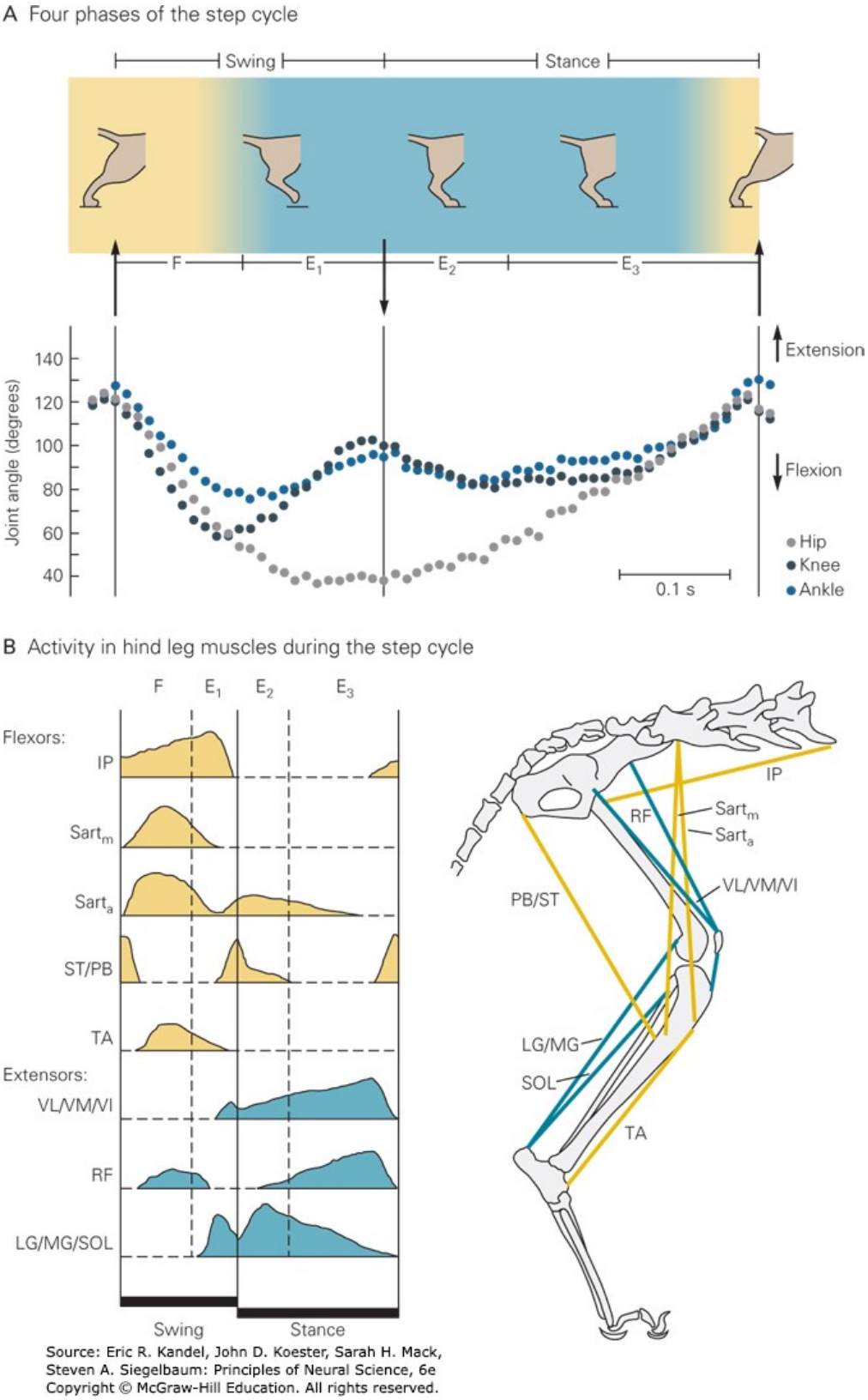
Figure 33–4

Stepping is produced by complex patterns of contractions in leg muscles.

A. The step cycle is divided into four phases. The flexion (**F**) and first extension ($\mathbf{E_1}$) phases occur during the swing phase, when the foot is off the ground, whereas second extension ($\mathbf{E_2}$) and third extension ($\mathbf{E_3}$) occur during the stance phase, when the foot contacts the ground. E_2 is characterized by flexion at the knee and ankle as the leg begins to bear the animal's weight. The contracting knee and ankle extensor muscles lengthen during this phase. (Adapted, with permission, from Engberg and Lundberg 1969.)

B. Profiles of electrical activity in some of the hind leg flexor (**yellow**) and extensor (**blue**) muscles in the cat during stepping. Although flexor and extensor muscles are generally active during the swing and stance phases, respectively, the overall pattern of activity is complex in both timing and amplitude. (Muscles: **IP**, iliopsoas; **LG** and **MG**, lateral and medial gastrocnemius; **PB**, posterior biceps; **RF**, rectus femoris; $\mathbf{Sart_m}$ and $\mathbf{Sart_a}$, medial

and anterior sartorius; **SOL**, soleus; **ST**, semitendinosus; **TA**, tibialis anterior; **VL**, **VM**, and **VI**, vastus lateralis, medialis, and intermedius.)



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Muscles within a single limb must be activated and coordinated in a precise spatiotemporal pattern (Figure 33–4B) so that the relative time of activation of different muscles, the duration of their activity, and the magnitude of that activity are coordinated to meet the demands of the environment

(*intralimb coordination*).

In the hindlimb, swing is initiated by flexion of the knee produced by activation of muscles such as the semitendinosus, followed shortly by activation of hip and ankle flexors (the F phase). The hip flexors continue to contract throughout swing, but the activity in the knee and ankle flexors is arrested as the leg extends in preparation for contact with the support surface (the E_1 phase). Activity in most extensor muscles begins at this stage, before the foot contacts the ground. This preparatory prestance phase signifies that the extensor muscle activity is centrally programmed and not simply the result of afferent feedback arising from contact of the foot with the ground.

Stance begins with contact of the foot or paw with the ground. During early stance (the E_2 phase), the knee and ankle joints flex due to the acceptance of the weight of the body, causing extensor muscles to lengthen at the same time they are contracting strongly (eccentric contraction). The spring-like yielding of these muscles as weight is accepted allows the body to move smoothly over the foot and is essential for establishing an efficient gait. During late stance (the E_3 phase), the hip, knee, and ankle all extend as the extensor muscles provide a propulsive force to move the body forward.

There is also a requirement for *interlimb coordination,* the precise coupling between different limbs. The coupling between the four legs in quadrupeds, for example, can vary quite substantially, dependent on both the speed of locomotion and the adopted gait (a walk, pace, trot, gallop, or bound). This is particularly true of the pattern of coupling between muscles of limbs of the same side (homolateral limbs) and for the diagonal limbs. The relation between limbs can be characterized by the phase difference, with 0 reflecting limbs that move together in phase and 0.5 limbs that move fully out of phase (ie, in opposite directions). During walking, activity between the homolateral limbs varies by a phase value of 0.25, and three legs are always in contact with the ground. During a trot, the diagonal limbs (eg, the left hindlimb and the right forelimb) are in phase, and the phase difference between homolateral limbs is 0.5. Phase relationships between limbs of the same girdle (ie, the forelimbs or hindlimbs) are more stable during gaits produced by activation of alternating limbs, such as a walk or trot (generally out of phase by 0.5 cycle), compared to synchronous locomotion like a gallop or bound (generally in-phase).

The appropriate generation of the intra- and interlimb coordination of activity and the adaptation of these patterns of activity according to circumstance is one of the major functions of the central nervous system during locomotion.

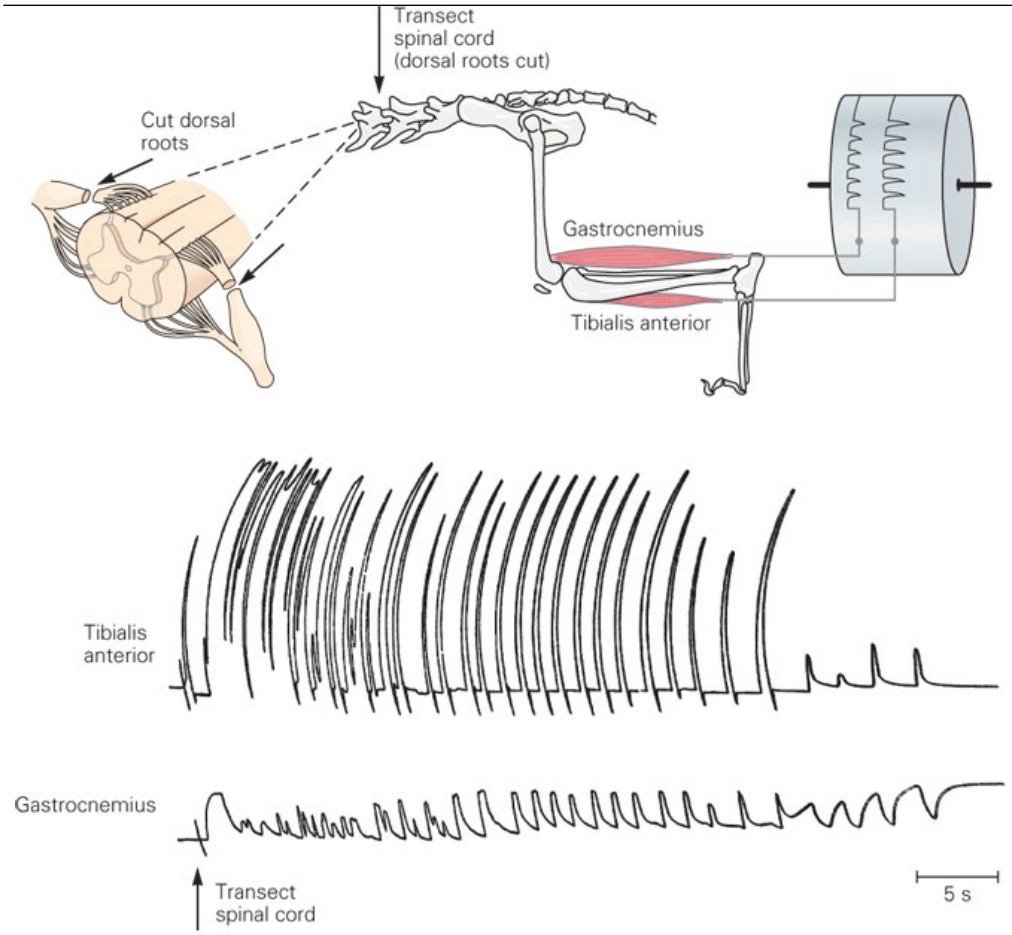
The Motor Pattern of Stepping Is Organized at the Spinal Level

While the entire nervous system is necessary for an animal to produce a rich behavioral repertory, the spinal cord is sufficient to generate both the rhythm underlying locomotion as well as much of the specific pattern of muscle activity required for intra- and interlimb coordination.

At the beginning of the 20th century, Graham Brown showed that the isolated spinal cord had the intrinsic capacity to generate a rudimentary alternating locomotor pattern around the ankle joint in the absence of sensory inputs to the spinal cord (Figure 33–5). He proposed that locomotor networks controlling flexor and extensor activity in the spinal cord were organized as half-centers such that when half of the circuit was active it would inhibit the other half. The center would be released from inhibition through some sort of synaptic or neuronal fatigue.

Figure 33–5

Rhythmic stepping is generated by spinal networks. The existence of intrinsic spinal networks was first demonstrated in 1911 by Thomas Graham Brown who developed an experimental preparation in which the dorsal roots were cut so that sensory information from the limb could not reach the spinal cord. The lower figure shows an original record from Graham Brown's study. Rhythmic alternating contractions of an ankle flexor (tibialis anterior) and an ankle extensor (gastrocnemius) are generated by the isolated spinal cord and persist for some time after the transection.



This ground-breaking observation was mostly ignored until the mid-1960s and early 1970s, when there began a period of intense study of the mechanisms by which the spinal cord could generate a rhythmical pattern of activity. Initial studies showed that stimulation of sensory fibers in spinal cats treated with L-DOPA (a precursor of the monoamine transmitters dopamine and norepinephrine) and nialamide (a drug that prolongs the action of L-DOPA) could produce short sequences of rhythmic activity in flexor and extensor motor neurons. It was further found that groups of interneurons in the spinal cord were activated in a reciprocal flexor and extensor pattern. This organizational feature was consistent with Graham Brown's theory that mutually inhibiting half-centers produced the alternating burst activity in flexor and extensor motor neurons.

In the half-center model, the spinal cord produces only the locomotor rhythm, while the pattern is sculpted by afferent feedback caused by the movement. However, this view was changed by experiments that demonstrated that a well-organized locomotor pattern could be observed in decerebrate and spinal cats walking on a treadmill after section of the dorsal roots, thus removing the afferent feedback (Figure 33–6A,B). Later experiments in chronic spinal cats in which rhythmic afferent feedback was abolished by preventing movement (Figure 33–6C) showed that spinal circuits were not only able to intrinsically produce a locomotor rhythm but could also produce some of the spatiotemporal details of the pattern of activity observed in the intact cat (Figure 33–6C).

Figure 33–6

Spinal circuits generate both a rhythm and a pattern.

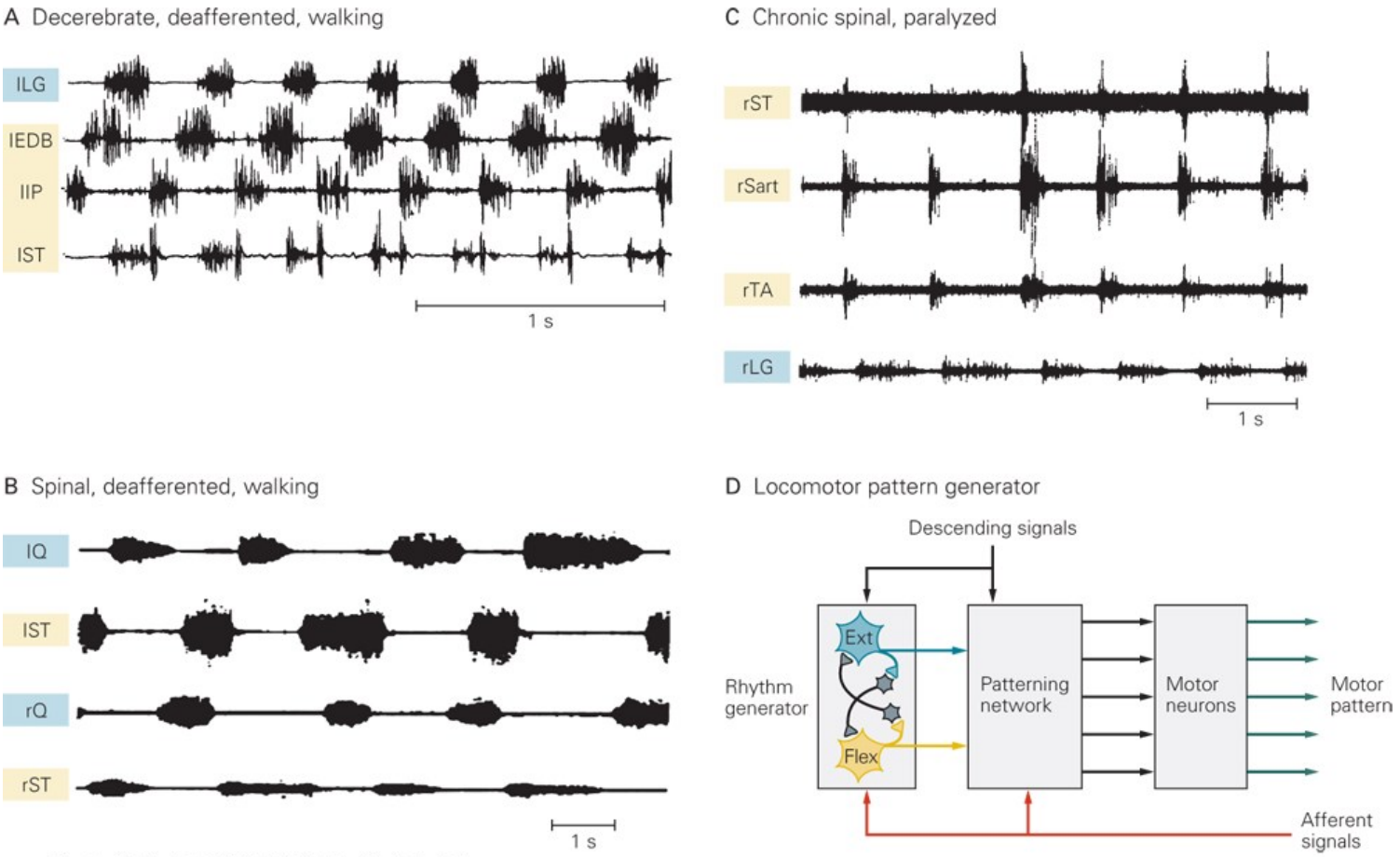
A. Even after removal of all sensory input to the spinal cord by cutting the dorsal roots, a decerebrate cat walking on a treadmill exhibits a complex motor pattern that is not just a simple alternation of flexor and extensor activity. (Abbreviations: **l**, left; **EDB**, extensor digitorum brevis; **LG**, lateral gastrocnemius; **IP**, iliopsoas; **ST**, semitendinosus.) (Adapted, with permission, from Grillner and Zangger 1984.)

B. Intravenous injection of L-DOPA and nialamide produces a well-organized locomotor pattern in an acute spinal cat with the dorsal roots cut.

(Abbreviation: **l**, left; **Q**, quadriceps; **r**, right.) (Adapted with permission from Grillner and Zangger 1979. Copyright © 1979 Springer Nature.)

C. Fictive locomotion in a chronic spinal paralyzed cat, demonstrating the typical pattern of activity in the semitendinosus, tibialis anterior (**TA**), lateral gastrocnemius (**LG**), and sartorius (**Sart**) muscles in intact cats. (**l**, left; **r**, right.) (Adapted from Pearson and Rossignol 1991.)

D. Conceptual model of a spinal locomotor central pattern generator (CPG) based on studies in decerebrate cats. The CPG model is formed of separate rhythm- and pattern-generating layers. Each of these layers can be modified by descending inputs and peripheral afferent information. (Adapted from Rybak et al. 2006.)



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These observations led to the important concept of a *central pattern generator* (CPG) that can generate both the rhythm and the pattern, independent of sensory inputs. Subsequent experiments led to the idea that separate components of the CPG are responsible for generating the underlying rhythm of locomotion within a limb and the spatiotemporal pattern of muscle action in the limb (Figure 33–6D). This notion was based on the observation that changes in rhythm and pattern can be influenced independently. Other studies have led to the concept that the CPG is modular, allowing independent control of activity around different joints.

Experiments in a variety of species have suggested that there are probably separate CPGs for each limb. For example, experiments using split belts, in which either the fore- and hindlimbs or the left and right limbs walk on separate treadmill belts, show that animals can independently modify step cycle duration in each pair of limbs. This organization would allow relatively simple descending commands to modify the coupling between each CPG and so to alter the pattern of the gait.

CPGs have now been identified and analyzed in many rhythmic motor systems, including those controlling over-ground locomotion, swimming, flying, respiration, and swallowing, in both invertebrates and vertebrates. In all vertebrates except higher primates and humans, a prominent locomotor pattern can be observed immediately after spinal transection when the spinal cord below the transection is activated with neuroactive drugs that

function as a substitute for the descending drive that normally activates the spinal locomotor networks (Box 33–1).

The Spinal Circuits Responsible for Locomotion Can Be Modified by Experience

Lesion of the spinal cord in otherwise intact adult mammals leads to paralysis. In the absence of any further intervention, such animals will regain only minimal locomotion. However, when quadrupedal animals with complete lesions of the thoracic spinal cord are trained daily, they regain a remarkable ability to use their hindlimbs to walk on a treadmill.

A similar improvement in locomotion can also be obtained from the application of noradrenergic agonists. Indeed, recordings of hindlimb joint angles and EMG activity from these animals show that the spinal cord isolated from all descending systems can generate most of the coordinating features in the hindlimb that are observed in intact animals. This training effect is believed to occur because of an activity-dependent reorganization of both internal spinal circuits and the modification of synaptic inputs from peripheral afferents that is specific to the training regimen. Indeed, cats can be trained specifically to either support their weight or to walk, without a transfer of motor skills between the two behaviors.

Spinal Locomotor Networks Are Organized Into Rhythm- and Pattern-Generation Circuits

The question of how the spinal cord generates the complex activity underlying locomotion has been one of intense study that has followed three complementary paths. The earliest experiments directed at this issue were performed in the cat and provided important information on the functional characteristics of different interneuronal populations. However, the complex nature of the mammalian spinal cord led researchers to identify models with fewer neurons in the spinal cord, such as the turtle and two aquatic preparations, the tadpole and the lamprey (Box 33–1). These latter two models have provided an excellent window into the organization of the spinal circuits involved in swimming and a foundation for studying rhythm and pattern generation in limbed animals. Last, the development of important molecular-genetic models in the mouse and the zebrafish has provided additional insights not available by more traditional methods.

The Swimming Central Pattern Generator

The lamprey—a jawless fish—swims like an eel with a wave of left–right bending traveling from front to back (Figure 33–3A). The spinal cord is made up of about 100 spinal segments, each containing neurons that can generate the rhythm and produce alternation between the two sides of the body. The rhythm is generated by interconnected glutamatergic excitatory neurons endowed with active membrane properties supporting rhythm generation. These glutamatergic neurons, which are the kernel in the swimming network, excite commissural inhibitory neurons, local inhibitory neurons, and motor neurons on the same side of the cord (Figure 33–7A).

Figure 33–7

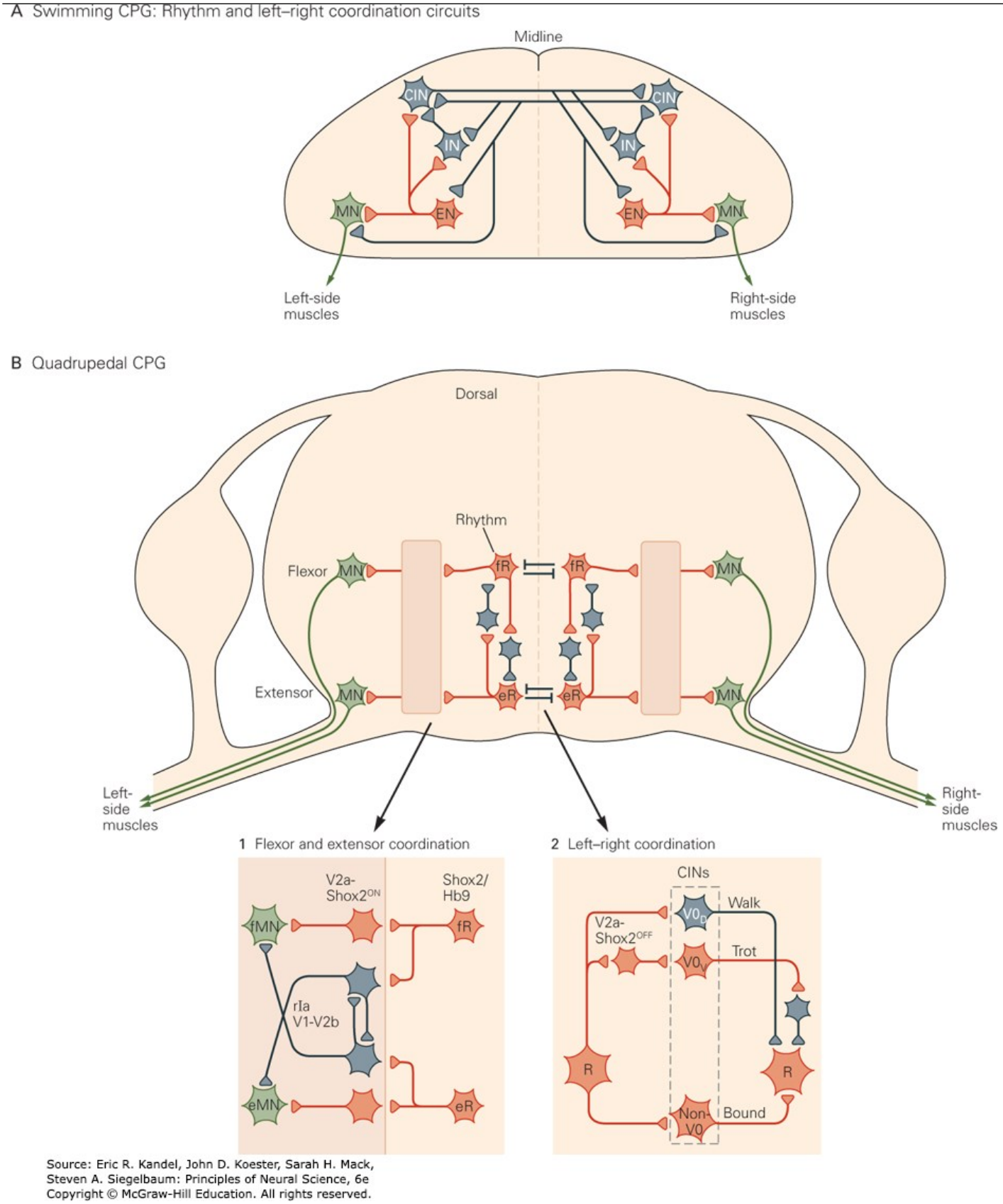
Spinal locomotor networks are organized into rhythm- and pattern-generation circuits with distinct cellular identities.

A. Circuit diagram of swimming central pattern generator (**CPG**) in the lamprey. Rhythm-generating circuits include excitatory interneurons (**EN**) that drive motor neurons (**MN**), inhibitory commissural interneurons (**CIN**) whose axons project to the other half of the cord, and local inhibitory interneurons (**IN**) with axons projecting on the same side of the cord. A single neuron in the diagram represents multiple neurons in the animal. **Gray neurons**, inhibitory; **red neurons**, excitatory. The vertical **dashed line** indicates the midline. (Data from Grillner 2006.)

B. General circuit diagram for limbed locomotion. Rhythm-generating circuits (**fR** and **eR**) composed of excitatory neurons on either side of the spinal cord drive flexor and extensor muscles on the same side through a pattern-generating layer (empty box). Rhythm-generating flexor (**fR**) and extensor (**eR**) neurons are reciprocally connected via inhibitory neurons and are connected across the midline via commissural interneurons (not shown) that mediate left–right coordination. The diagram shows one spinal segment. (Abbreviation: **MN**, motor neurons.) (Data from Kiehn 2016.)

B1. Flexor and extensor alternation is controlled at multiple levels in the locomotor network. One synapse away from flexor (**f**) and extensor (**e**) motor neurons (**MN**) are Ia-inhibitory interneurons, which reciprocally innervate antagonist motor neurons and each other (Chapter 32). The rIa neurons belong to two major groups of molecularly defined inhibitory neurons, V1 and V2b, in the ventral spinal cord. Excitatory neurons with different molecular markers (including V2a-Shox2^{ON}) provide premotor rhythmic excitation of motor neurons. Rhythm-generating Shox2^{ON} or Hb9 neurons (**fR** and **eR**) drive both inhibitory and excitatory premotor neurons. (Data from Kiehn 2016.)

B2. Rhythm-generating circuits drive left–right coordinating circuits composed of a dual inhibitory pathway involved in alternation and a single excitatory pathway involved in synchrony. The dual inhibitory pathway is composed of inhibitory $V0_D$ commissural neurons that directly inhibit rhythm generation on the other side and excitatory $V0_V$ commissural neurons that indirectly inhibit locomotor networks on the other side. The inhibitory $V0_D$ commissural neuron pathway controls the alternating gait walk. A population of V2a excitatory neurons is part of the left–right alternating circuit and connects to $V0_V$ commissural neurons. This pathway controls the alternating gait trot. Rhythm-generation circuits also drive a left–right synchronizing circuit possibly involved in bound, composed of non-V0 neurons. Only the projections from the left to the right side are shown. (Data from Kiehn 2016.)



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The commissural interneurons, whose axons cross the midline, inhibit the contralateral interneurons involved in generating the alternating rhythm as well as contralateral motor neurons (Figure 33–7A). Cellular mechanisms contribute to phase switching in the network (Box 33–2). For example, Ca^{2+}

entry triggered by bursting in glutamatergic neurons activates their calcium-activated K^+ channels. The opening of these channels hyperpolarizes the cells and enables termination of the burst. The termination of bursting on one side activates the other side by the commissural interneurons, thus allowing the contralateral rhythm-generating interneurons and motor neurons to become active. To enable coordination along the body, the segmental networks are connected through long-distance descending projections of excitatory and inhibitory neurons. This basic organization of interconnected excitatory neurons, inhibitory commissural neurons, and a rostrocaudal connectivity gradient for intersegmental coordination is also found in the tadpole and is possibly common to other swimming species.

Box 33–2 Neuronal Ion Channels Contribute to Central Pattern Generator Function

Neuronal membrane properties make an important contribution to the function of the central pattern generator (CPG). Neurons have a variety of K^+, Na^+, and Ca^{2+} channels that determine their activity and response to synaptic inputs. Studies of CPGs in diverse experimental models have shown that ion channels may be important for promoting rhythmicity, through bursting properties, or patterning, through ion channels that affect phase transitions or the rate of neuronal discharge.

Bursting and Plateau Properties Amplify Cellular Responses

Membrane properties that produce bursting allow cells to produce sustained oscillations in the absence of synaptic inputs. These properties are either intrinsic, as in cells in the sinusoidal node in the heart, or conditional, dependent on the presence of certain neurotransmitters. In some small motor CPGs (such as the pyloric network in the stomatogastric ganglion, which controls rhythmic movements in the gut of crustaceans), intrinsic bursting properties are essential for generating the rhythm.

Conditional bursting triggered by glutaminergic activation of *N*-methyl-D-aspartate (NMDA) receptors has been described in spinal cord interneurons and motor neurons in lamprey, rodents, and amphibians. In the lamprey, bursting due to NMDA receptor activation plays a role in generating swimming. In mammals, it is as yet uncertain whether NMDA receptor–induced bursting is essential for rhythm generation, although it may facilitate excitatory synaptic inputs in the circuit.

Plateau potential is another membrane property that may cause a neuron's membrane potential to jump to a depolarized state that will support action potential firing without further increase in the excitatory drive. Plateau properties amplify and prolong the effect of synaptic excitatory inputs and may promote rhythm generation and motor output. Plateau properties are generated by activation of slowly inactivating L-type Ca^{2+} channels or slowly inactivating Na^+ channels. These channels have been found in vertebrate interneurons and motor neurons. The expression of plateau properties mediated by L-type Ca^{2+} channels in motor neurons is controlled by neuromodulatory neurotransmitters, such as serotonin and norepinephrine. The slowly inactivating Na^+ channels are generally not regulated by neurotransmitters. Blockage of these channels decreases rhythm generation.

Phase Transitions May Be Regulated by Voltage-Gated Ion Channel Activation

Reciprocal inhibition between neurons is a common design in locomotor circuits; ion channels activated in the subthreshold spike range may enhance or delay phase transitions by such inhibition. Three types of voltage-gated channels are involved: a transient low threshold Ca^{2+} channel, cation-nonselective permeable hyperpolarization-activated cyclic nucleotide-gated (HCN) channels, and transient K^+ channels.

The transient low-threshold Ca^{2+} channels are inactivated at membrane potentials around rest. Transient inhibitory synaptic inputs remove the inactivation. When released from synaptic inhibition, activation of low-threshold Ca^{2+} channels will cause a short-lasting rebound excitation before the channels inactivate again. In the lamprey, spinal cord activation of metabotropic $GABA_B$ receptors depresses low-threshold Ca^{2+} channels involved in producing the swimming motor pattern. The suppression leads to a longer hyperpolarized phase and therefore to a slower alternation between antagonistic muscles, a possible mechanism for the slowing of swimming seen following $GABA_B$ receptor activation.

HCN channels are found in many CPG neurons and motor neurons and may help neurons escape from inhibition. They are activated by hyperpolarization, such as occurs during synaptic inhibition. Their activation depolarizes the cell, counteracting the hyperpolarization. Finally, the kinetics of their activation and deactivation are slow, so they stay open for some time after the hyperpolarization is released. The channel kinetics affect the integrative properties of the cell in two important ways. First, the depolarization caused by the channel opening limits the effect of

sustained inhibitory inputs and helps the cell escape from inhibition. Second, the slow closing following synaptic inhibition leads to a rebound excitation promoting the next burst.

Voltage-gated A-type transient K^+ channels are usually inactivated at resting membrane potential. Hyperpolarization removes the resting inactivation, and subsequent depolarization will cause a transient activation of the channel. Their activation will therefore delay the onset of the next burst.

Regulation of Spiking Controls How Much Cells Are Activated

A number of different ion channels play a role in regulating the firing rate of a cell. Activation and inactivation kinetics of Na^+ channels are factors. Other important channels are sodium- and calcium-activated K^+ channels. The effect of activation of these K^+ channels is often seen as a slow after-hyperpolarization following an action potential or a train of action potentials. Activation of these channels therefore causes spike train adaptation and postactivation inhibition, which contribute to burst termination.

Molecular and genetic approaches have expanded our understanding of the functional organization of CPGs in fish and identified two groups of glutamatergic interneurons—a group of commissural neurons and a group of ipsilaterally projecting neurons—that are involved in rhythm generation but at different speeds of locomotion. In adult zebrafish, the rhythm-generating circuit is composed of three functional classes of excitatory neurons that drive slow, intermediate, and fast pools of motor neurons that are selectively recruited as the speed of swimming increases.

The Quadrupedal Central Pattern Generator

The CPG controlling quadrupedal locomotion has added organizational complexity compared to the swimming CPG since it must generate both the rhythm and the pattern that involves the sequential flexor-extensor alternation of muscles around different joints within a limb (Figure 33–4B), as well as left–right coordination and coordination between the forelimbs and hindlimbs. Circuits controlling the forelimb are located in the cervical enlargement, whereas circuits controlling the hindlimb are located in the lower thoracic and lumbar spinal cord.

As in the CPG that generates rhythmical swimming activity, glutamatergic excitatory interneurons are involved in quadrupedal rhythm generation. Using advanced mouse genetics together with a molecular code that builds on expression of gene-regulating transcription factors that differentiate spinal neurons into classes with specific projection and transmitter phenotypes (Box 33–3), it has now been shown that the core of the rhythm-generating circuits in rodents includes two nonoverlapping groups of molecularly distinct glutamatergic neurons ($Shox2^{ON}$ and Hb9; Figure 33–7B1).

Box 33–3 Molecular-Genetics Combined With Anatomical, Electrophysiological, and Behavioral Analyses Are Used to Unravel the Locomotor Network Organization

To unravel the functional organization of the large neuronal networks in the spinal cord, researchers have used molecular-genetic–driven network analysis to take advantage of a molecular code that determines the spatial layout of the spinal locomotor networks.

It has been well documented that motor neurons develop and differentiate according to a genetic code expressed in the embryonic spinal cord (Chapter 45). This feature extends also to the development of spinal interneurons, which can be identified by different transcription factors (Table 33–1). The cardinal classes of interneuronal types belong to dorsally located interneurons (dI1–dI6) and ventrally located interneurons (V0–V3), with further subdivision within these categories (eg, $V0_D$ and $V0_V$, V2a-$Shox2^{Off}$, V2a-$Shox^{On}$) where a combination of transcription factors defines these subtypes (Table 33–1). Each group of interneurons has specific transmitter content and characteristic axonal projection patterns.

The ability to manipulate these specific interneuron types gives an unparalleled opportunity to examine the functional contribution of specific subsets of interneurons in the mouse or zebrafish that is not possible in species such as the cat. The molecular code of the spinal cord neurons is used to mark cells with a marker protein such as green fluorescent protein or for the expression of proteins that allow for cell type-specific ablation or activation/inactivation of cells types. Such studies have ascribed specific locomotor functions to the dI3, V0–V3, and Hb9 cells, all molecularly differentiated classes of neurons (Table 33–1).

Table 33–1

Developmental Molecular Codes Specify the Identity of Spinal Neurons in the Spinal Cord

Postmitotic transcription factors	Neuron type	Transmitters
Islt1/Tlx3	dI3	Glutamate
Pax2/7	$V0_D$	GABA/glycine
Evx1	$V0_V$	Glutamate
Evx1/Pitx2	$V0_C$	Acetylcholine
Evx1/Pitx2	$V0_D$	Glutamate
En1	V1	GABA/glycine
Chx10	V2a-$Shox2^{Off}$	Glutamate
Chx10/Shox2	V2a-$Shox2^{ON}$	Glutamate
GATA2/3	V2b	GABA/glycine
Sox1	V2c	GABA/glycine
Shox2	V2d	Glutamate
Hb9/Islt1-2	MN	Acetylcholine
Hb9	Hb9	Glutamate
Sim1	$V3_D$	Glutamate
Sim1	$V3_V$	Glutamate

Chx10, Ceh-10 homeodomain-containing homolog; Evx1, even skipped homeobox 1; En1, engrailed 1; GABA, γ-aminobutyric acid; GATA2/3, gata protein; Hb9, homeobox 9; Islt1-2, ISL1-2 transcription factor; Pax, paired box gene; Pitx2, paired-like homeodomain transcription factor 2; Sim1, single-minded homolog 1; MN, motor neuron; Shox2, Short stature homeobox 2; Sox1, SRY box-containing gene 1; Tlx1/3, T cell leukemia, homeobox 1/3.

Source: Adapted from Jessell 2000, Goulding 2009, Dougherty et al. 2013.

The flexor (f) and extensor (e) rhythm-generating (R) circuits, which are connected by reciprocal inhibition (Figure 33–7B), drive other neurons in the locomotor network into rhythmicity and provide the rhythmic excitation for motor neurons (Figure 33–7B). As has been observed in the swimming CPG, ionic channels are also likely to contribute to rhythm generation and phase switching in the quadrupedal CPG.

The Flexor and Extensor Coordination Circuit

Flexor and extensor activity must be coordinated around joints (eg, hip-knee-ankle-toe in the hindlimb) to control the limb movement in a precise manner. Accordingly, the flexor-extensor alternation around the different joints is not simultaneous but has a sequential pattern, which suggests that

multiple flexor-extensor alternating circuits are needed to time muscle actions in a limb. The basic flexor-extensor alternation circuits are organized in flexor and extensor modules composed of inhibitory and excitatory interneurons that are one synapse away from the flexor and extensor motor neurons they control (Figure 33–7B,B1).

Inhibitory and excitatory neurons in the module provide alternating inhibition and excitation of motor neurons. The reciprocally connected inhibitory Ia interneurons (Chapter 32) are part of the flexor and extensor modules providing the direct motor neuron inhibition in a reciprocal fashion (rIa in Figure 33–7B1). The rIas belong to the molecularly defined inhibitory V1 and V2b neurons (Figure 33–7B1). The excitatory neurons that directly excite motor neurons during locomotion are likely to belong to multiple classes of neurons in the spinal cord, including V2a-Shox2^{ON} and the dI3 neurons (Figure 33–7B1).

In this basic scheme, the flexor-extensor modules are driven by flexor (fR in Figure 33–7B1) and extensor rhythm-generating circuits (eR in Figure 33–7B1), which themselves are reciprocally connected via inhibitory neurons (Figure 33–7B), resulting in their out-of-phase activity.

Left–Right Coordination

Left–right alternation, for both swimming and over-ground locomotion, depends on crossed inhibition produced in two ways: directly by inhibitory commissural neurons or indirectly by excitatory commissural neurons, each of which acts on premotor inhibitory neurons (Figure 33–7B2). This dual inhibitory system has a counterpart in one specific neuronal population, the V0 commissural neurons (Figure 33–7B2). Ablation of V0 neurons results in loss of left–right alternation at all speeds of locomotion. The inhibitory dorsal class of V0 neurons ($V0_D$), which makes up about half of the V0 population, controls alternating locomotion during walking, whereas the excitatory ventral class of V0 neurons ($V0_V$), which makes up the remaining half of V0 neurons, controls alternating locomotion during trot. The dual system thus serves a speed-dependent role in coordinating alternating gaits (walk and trot). Separate excitatory non-V0 commissural neurons—possibly the ventral V3 neurons (Box 33–3)—are responsible for synchrony in gaits such as bound and gallop (Figure 33–7B2).

The dual-mode left–right alternating pathways are driven directly by the rhythm-generating neurons or indirectly by other non–rhythm-generating excitatory neurons, including the V2a-Shox2^{Off} neurons that are recruited at high speeds of locomotion and synaptically connect to the $V0_V$ neurons. The left–right synchronous pathways are active at higher speeds of locomotion when the alternating system is suppressed or less active.

The speed-dependent changes in the left–right alternation circuits in the rodent are an example of functional reorganization of the vertebrate locomotor network needed to produce diverse motor outputs. Similar dynamic circuit reorganization has also been demonstrated in zebrafish and in studies of rhythmic networks in invertebrates, such as the stomatogastric ganglion controlling gut movements in crustaceans, where different functional networks emerge from a common CPG network.

Interlimb Coordination

The organization of the networks that couple fore- and hindlimbs is not known in detail, but experiments using both lesion and genetic ablation suggest that these pathways involve both inhibitory and excitatory intersegmental connections.

Somatosensory Inputs From Moving Limbs Modulate Locomotion

Even though the CPG can produce the precise timing and phasing of the muscle activity needed to walk, this central pattern is normally modulated by sensory signals from the moving limbs. Two types of sensory input modulate the CPG activity: proprioceptive information generated by the active movement of the limb and tactile information generated when the moving limb meets an obstacle in the surrounding environment.

Proprioception Regulates the Timing and Amplitude of Stepping

One of the clearest indications that somatosensory signals from moving limbs regulate the locomotor cycle is that the rate of locomotion in spinal and decerebrate cats matches the speed of the motorized treadmill belt on which they walk. As the stepping rate increases, the stance phase becomes shorter while the swing phase remains relatively constant.

This observation suggests that some form of sensory input from the moving limb signals the end of the stance phase and thus leads to the initiation of

the swing phase. The sensory information from the moving limb is generated by proprioceptors in the muscles and joints. These proprioceptors include stretch-sensitive muscle spindles in the hip and force-sensitive Golgi tendon organs in the ankle that are particularly important for facilitating locomotor phase transition.

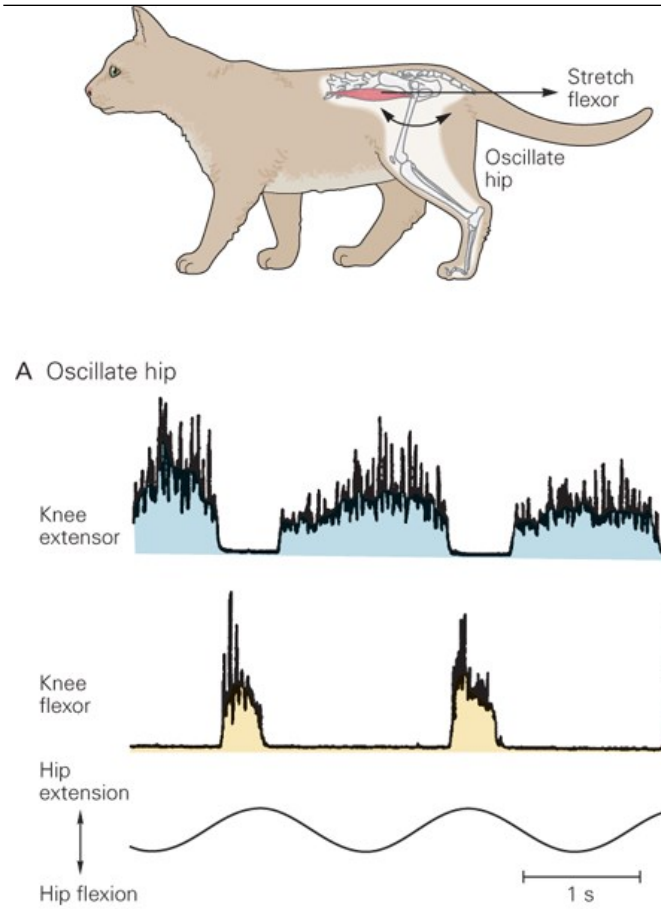
The influence from the hip was noticed already by Sherrington, who showed that rapid extension at the hip joint leads to contractions in the hip flexor muscles of chronic spinal cats and dogs. More recent studies have found that preventing hip extension in a limb suppresses stepping in that limb, whereas rhythmically moving the hip in an immobilized cat can entrain the locomotor rhythm; that is, the stretching of the hip muscles causes the timing of the motor output to match the rhythm of the externally imposed movements (Figure 33–8A). The stretching also activates flexor muscle spindles and mimics the lengthening that occurs at the end of the stance phase, thus inhibiting extensor activity and facilitating activation of the flexor rhythm-generating circuits in the spinal cord (Figure 33–8B).

Figure 33–8

Hip extension initiates the transition from stance to swing phase of walking.

A. In an immobilized decerebrate cat, passive oscillating movement around the hip joint initiates and entrains the fictive locomotor pattern in knee extensor and flexor motor neurons. The flexor electromyogram (EMG) bursts correspond to the swing phase and are generated when the hip is extended. (Adapted, with permission, from Kriellaars et al. 1994.)

B. In a walking decerebrate cat, stretching of the hip flexor muscle (iliopsoas) inhibits knee extensor EMG activity, allowing knee flexor activity to begin earlier. The **arrow** in the knee flexor record indicates when activity in the muscle would have begun had the hip flexor muscle not been stretched. Activation of sensory fibers from muscle spindles in the hip flexor muscle is responsible for this effect. (Adapted, with permission, from Hiebert et al. 1996.)



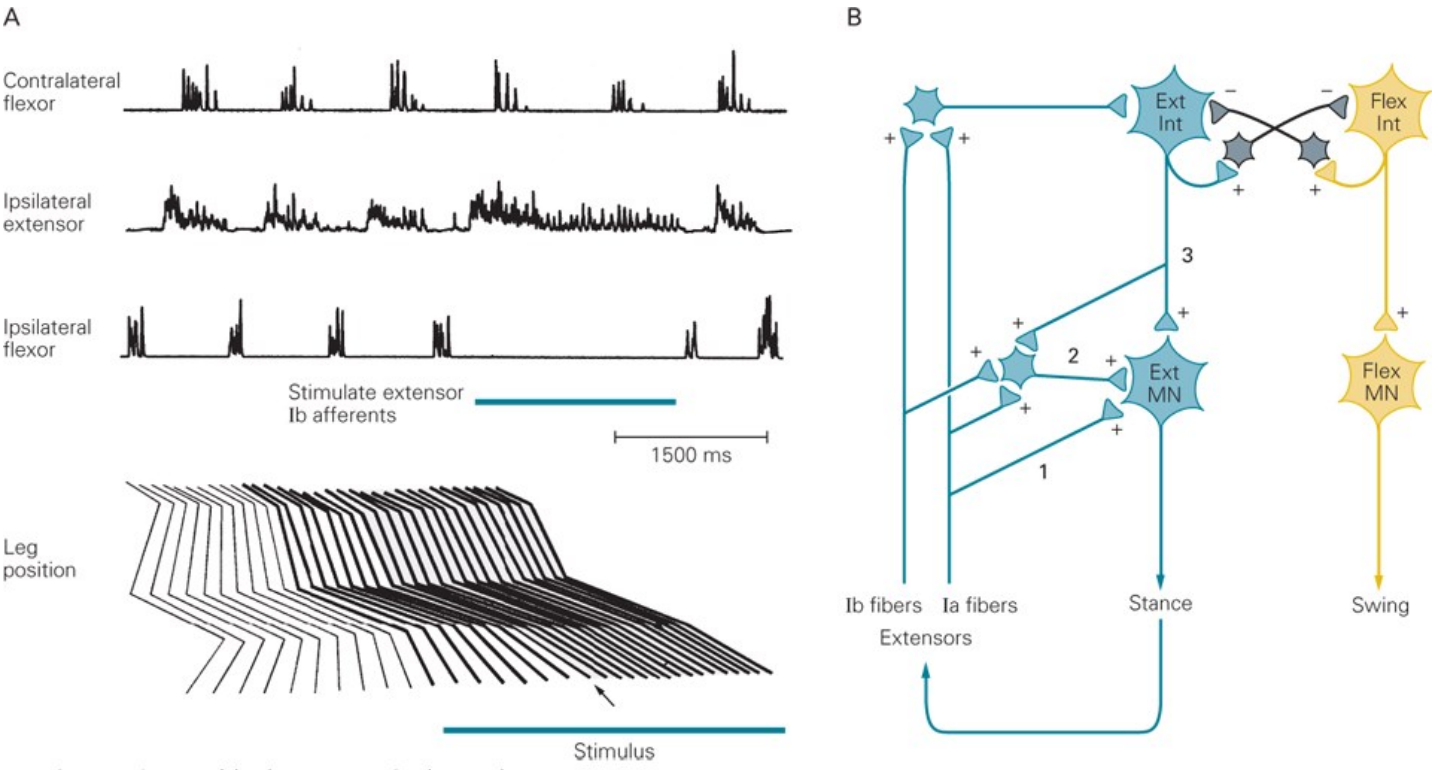
Activation of sensory fibers from Golgi tendon organs and muscle spindles in ankle extensor muscles prolongs the stance phase, often delaying the onset of the swing phase until the stimulus has ended (Figure 33–9A). Sensory fibers from both types of receptors are active during stance, with the intensity of the signal from the Golgi tendon organs being strongly related to the load carried by the leg. Golgi tendon organs have inhibitory actions on ankle extensor motor neurons when the body is at rest (Chapter 32) but an excitatory action during walking. This reversal of the sign of the reflex is caused by inhibition of inhibitory interneuron pathways together with a release of excitatory pathways during locomotion. The functional consequence of this reflex reversal during locomotion is that the swing phase is not initiated until the extensor muscles are unloaded and the forces exerted by these muscles are low, as signaled by a decrease in activity from the Golgi tendon organs near the end of stance.

Figure 33–9

The swing phase of walking is initiated by sensory feedback from extensor muscles.

A. In a decerebrate cat, electrical stimulation of group I sensory fibers from ankle extensor muscles inhibits the electromyogram burst in ipsilateral flexors and prolongs the burst in the ipsilateral extensors during walking. The timing of contralateral flexor activity is not altered. Stimulating group I fibers from ankle extensors prevents initiation of the swing phase, as can be seen in the position of the leg during the time the fibers were stimulated. The **arrow** shows the point at which the swing phase would normally have occurred had the ankle extensor afferents not been stimulated. (Adapted, with permission, from Whelan, Hiebert, and Pearson 1995. Copyright © Springer-Verlag 1995.)

B. Mutually inhibiting groups of extensor (**Ext**) and flexor (**Flex**) interneurons (**Int**) constitute a rhythm generator in the afferent pathway regulating the stance phase. Feedback from extensor muscles increases the level of activity in extensor motor neurons (**MN**) during the stance phase and maintains extensor activity when the extensor muscles are loaded. The feedback is relayed through three excitatory (**+**) pathways: (**1**) monosynaptic connections from Ia fibers to extensor motor neurons; (**2**) disynaptic connections from Ia and Ib fibers to extensor motor neurons; and (**3**) polysynaptic excitatory pathways that act through the extensor rhythm generator to maintain the extensor motor neurons active in stance phase.



Source: Eric R. Kandel, John D. Koester, Sarah H. Mack, Steven A. Siegelbaum: Principles of Neural Science, 6e

In sum, proprioceptive signals from the ankle extensor muscles and hip flexor muscles work synergistically to facilitate the stance-to-swing phase transition. In the late stance phase, when the limb is unloaded, as inhibitory signals from Golgi tendon organs wane, their effects on extensor rhythm generation declines, while at the same time the activity in muscle afferents around the hip joint is increased, facilitating activity in flexor rhythm generation.

At least three excitatory pathways transmit sensory information from extensor muscles to extensor motor neurons during walking: a monosynaptic pathway from primary muscle spindles (group Ia afferents), a disynaptic pathway from primary muscle spindles and Golgi tendon organs (group Ia and Ib afferents), and a polysynaptic pathway from primary muscle spindles and Golgi tendon organs that includes interneurons in the extensor rhythm generator (Figure 33–9B). These pathways all contribute to phase transition from stance to swing when the ankle is unloaded and maintain extensors in stance phase when the ankle is loaded.

In addition to regulating the transition from stance to swing, proprioceptive information from muscle spindles and Golgi tendon organs contributes significantly to the generation of burst activity in extensor motor neurons. Reducing this sensory input in cats diminishes the level of extensor activity

by more than half; in humans, it has been estimated that up to 30% of the activity of ankle extensor motor neurons is caused by feedback from the extensor muscles.

Mechanoreceptors in the Skin Allow Stepping to Adjust to Unexpected Obstacles

Mechanoreceptors in the skin, including some nociceptors, have a powerful influence on the CPG for walking. One important function of these receptors is to detect obstacles and adjust stepping movements to avoid them. A well-studied example is the corrective reaction to stumbling in cats.

A mild mechanical stimulus applied to the dorsal part of the paw during the swing phase produces excitation of flexor motor neurons and inhibition of extensor motor neurons, leading to rapid flexion of the paw away from the stimulus and elevation of the leg in an attempt to step over the object. Because this corrective response is readily observed in spinal cats, it must be produced to a large extent by circuits entirely contained within the spinal cord.

One of the interesting features of the corrective reaction is that corrective flexion movements are produced only if the paw is stimulated during the swing phase. An identical stimulus applied during the stance phase produces the opposite response—excitation of extensor muscles that reinforces the ongoing extensor activity. This extensor action is appropriate; if a flexion reflex were produced during the stance phase, the animal might collapse because it is being supported by the limb. This is an example of a phase-dependent reflex reversal. The same stimulus can excite one group of motor neurons during one phase of locomotion while activating the antagonist motor neurons during another phase.

Supraspinal Structures Are Responsible for Initiation and Adaptive Control of Stepping

Although the basic motor patterns for locomotion are generated in the spinal cord, the initiation, selection, and planning of locomotion require activation of supraspinal structures, including the brain stem, the basal ganglia, cerebellum, and cerebral cortex. Supraspinal regulation of stepping provides a number of behavioral modifications that cannot be mediated by spinal circuits alone. These include the voluntary initiation of locomotion and the regulation of speed; postural regulation, including weight support, balance, and interlimb coordination; and the planning and execution of anticipatory modifications of gait, particularly visually guided modifications.

Midbrain Nuclei Initiate and Maintain Locomotion and Control Speed

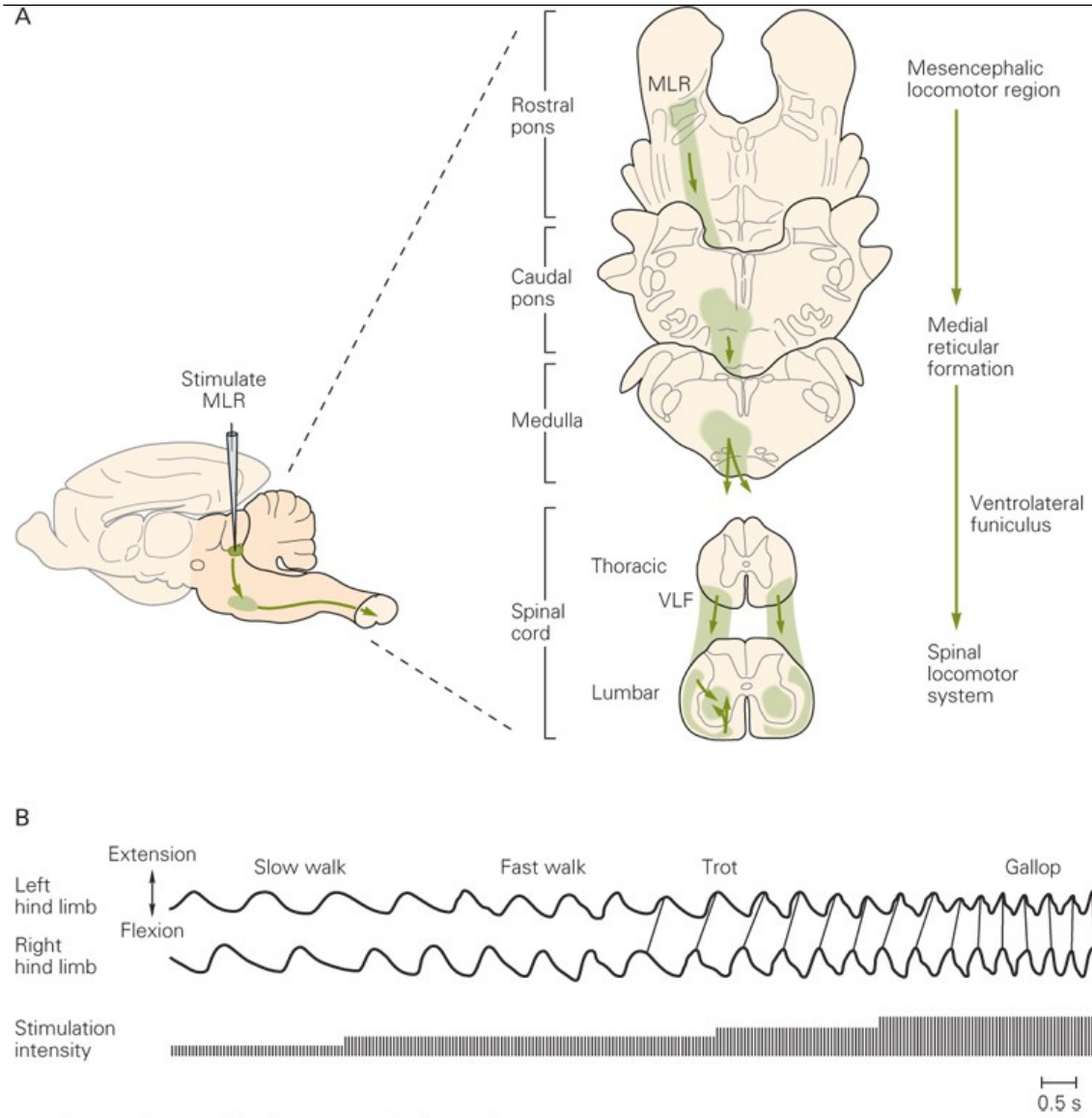
The locomotor networks in the spinal cord require a command or start signal from supraspinal regions to initiate and maintain their activity. The major neuronal structure involved in the initiation in vertebrates is a region in the midbrain called the mesencephalic locomotor region (MLR). The MLR was first identified in cats as a unitary region localized in or around the cuneiform nucleus, just below the inferior colliculus. Tonic electrical stimulation in this area in the resting animal increased postural tonus so that the animal stood up and then started to walk. As the intensity of stimulation rose, the speed of locomotion increased and alternating gaits switched to synchronous gaits such as gallop or bound (Figure 33–10).

Figure 33–10

The mesencephalic locomotor region initiates locomotion.

A. Electrical stimulation of the mesencephalic locomotor region (**MLR**) in the cat initiates locomotion by activating neurons in the medial reticular formation whose axons descend in the ventrolateral funiculus (**VLF**) to the spinal locomotor system.

B. When the strength of electrical stimulation of the MLR in a decerebrate cat walking on a treadmill is gradually increased, the gait and rate of stepping change from slow walking to trotting and finally to galloping. As the cat progresses from trotting to galloping, the hind limbs shift from alternating to in-phase activity. (Adapted from Shik et al. 1966.)



Later studies with electrical stimulation confirmed the presence of the MLR in all vertebrates, suggesting that the MLR is evolutionarily conserved from the oldest vertebrates to humans. These studies have pointed to two midbrain structures as part of the MLR (Figure 33–11A): the cuneiform nucleus (CNF) and the more ventrally located pedunculopontine nucleus (PPN) (Figure 33–11A). These two nuclei differ in the types of neurons they contain.

Figure 33–11

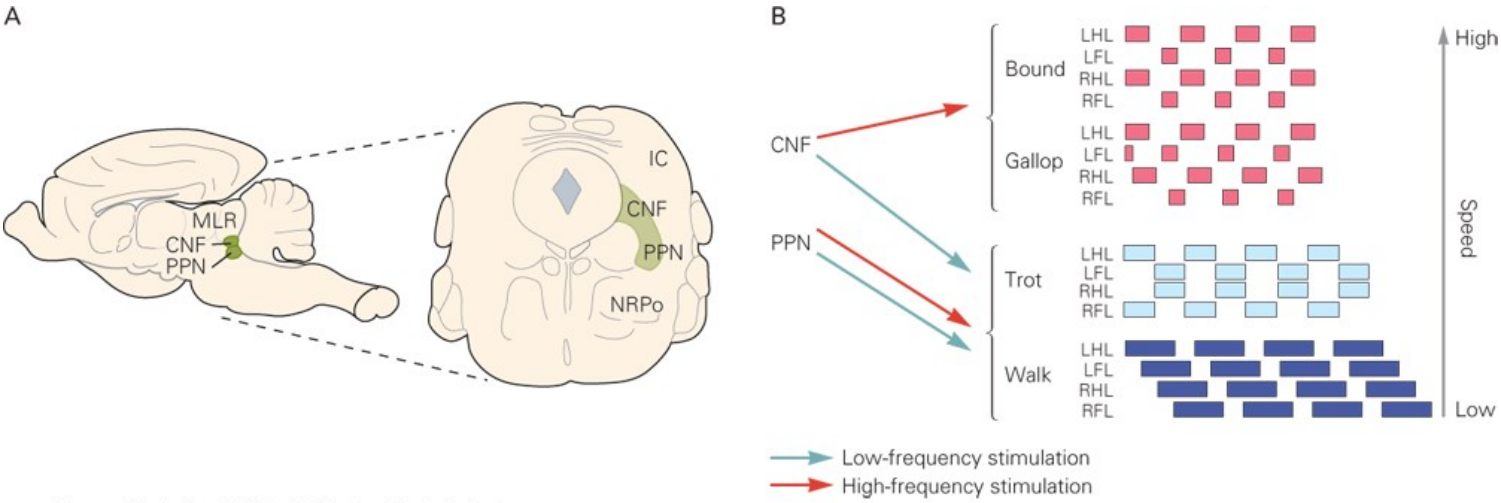
The mesencephalic locomotor region is composed of dual midbrain glutamatergic nuclei that control initiation of locomotion, speed and gait regulation, and context-dependent selection of locomotion.

A. *Left*: The site of the localization of mesencephalic locomotor region (**MLR**) in the midbrain of the mouse. *Right:* Transverse section shows that the MLR is composed of the cuneiform nucleus (**CNF**) and the pedunculopontine nucleus (**PPN**) in the midbrain, lateral to the cerebral aqueduct, and dorsal to the nucleus reticularis pontis oralis (**NRPo**). Glutamatergic, GABAergic, and cholinergic neurons are intermingled in the CNF and PPN. (Abbreviation: **IC**, inferior colliculus).

B. Effect in mice of optical stimulation of glutamatergic cells in the CNF or PPN that have been transfected with the light-sensitive channel, channelrhodopsin 2. Stimulation at low and high frequencies in the PPN leads only to alternating gaits—walking and trotting. Low-frequency

simulation in the CNF likewise results only in slow, exploratory locomotion, while high-frequency stimulation evokes the synchronous gaits gallop and bound corresponding to escape locomotion.

The different types of gaits are shown as idealized diagrams from low to high speeds of locomotion. Filled boxes represent the stance phase; open spaces the swing phase. Walk is characterized by periods of support by three or four feet simultaneously. Trot is characterized by simultaneous activity in the diagonal fore and hindlimbs. Gallop is characterized by the forelimbs moving slightly out of phase and hind limbs being almost in phase. Bound is characterized by hind limbs and forelimbs moving simultaneously and forelimb and hindlimb out of phase. (Abbreviations: **LFL**, left forelimb; **LHL**, left hindlimb; **RFL**, right forelimb; **RHL**, right hindlimb.) (Adapted from data in Caggiano et al. 2018.)



Long-range projection neurons in the CNF are excitatory and use glutamate as their neurotransmitter, whereas those in the PPN are both glutamatergic and cholinergic. In both nuclei, the excitatory neurons are intermingled with local GABAergic interneurons. Electrical stimulation has, however, been unable to determine which nucleus or which types of neurons are involved in the initiation of locomotion and speed control. However, the use of selective activation and inactivation of neurotransmitter-specific CNF and PPN neurons suggests that the two nuclei play specific roles in speed control and gait selection of locomotion (Figure 33–11B). Glutamatergic neurons in both PPN and CNF are sufficient for supporting alternating locomotion at slower speeds, such as walking and trot, while glutamatergic neurons in the CNF are necessary for high-speed locomotion, such as gallop and bound, characteristic of escape locomotion. Expression of these gaits is dependent on the stimulation frequency, possibly reflecting the effect of firing frequency in the intact animal.

The role of cholinergic PPN neurons for locomotion is less well understood. In mammals, they do not seem to have a strong role in maintaining locomotion.

These roles of glutamatergic CNF and PPN neurons in locomotor control may also be reflected in the different inputs. PPN neurons receive strong input from the basal ganglia, specifically the substantia nigra pars reticulata, globus pallidus pars interna, and subthalamic nucleus, as well as from sensorimotor and frontal cortex. Additionally, the PPN receives sensorimotor information from many nuclei in the midbrain and brain stem. The nucleus may therefore serve as a hub for integrating information from many brain structures, possibly leading to the release of slower exploratory locomotion. In contrast, the input to neurons in CNF is much more restricted and arises principally from structures that may be involved in escape responses. The MLR is therefore composed of two regions that act together to select context-dependent locomotor behavior.

Another brain area that evokes locomotion when stimulated is the subthalamic (or diencephalic) locomotor region (to be distinguished from the subthalamic nucleus). This region includes nuclei in the dorsal and lateral hypothalamus involved in various homeostatic features such as regulating feeding. Neurons in these areas project to neurons in the reticular formation and bypass the PPN and CNF, suggesting a parallel pathway for initiating locomotion, possibly driven by the need to find food.

Midbrain Nuclei That Initiate Locomotion Project to Brain Stem Neurons

The excitatory signals from CNF and PPN are relayed indirectly to the spinal cord by way of neurons in the brain stem reticular formation, which

provide the final command signal to the locomotor networks in the spinal cord. The identity of these neurons is only partly known. In general terms, two transmitter-defined pathways are involved: glutamatergic and serotonergic.

The glutamatergic locomotor pathways probably have multiple origins in the brain stem reticular formation, forming parallel descending pathways. They project directly or indirectly via a chain of intersegmental (propriospinal) glutamatergic interneurons to locomotor neurons in the spinal cord (Figure 33–10A). Reticulospinal neurons also participate in regulating the postural activity that is needed for the animal to locomote (see later discussion).

Evidence for the existence of a serotonergic locomotor pathway in mammals is restricted to experiments in rats that have shown the involvement of serotonergic neurons in the caudal brain stem. The mechanisms by which the final command signals from the brain stem to the spinal cord activate the spinal locomotor networks, maintain their activity, and allow the expression of different gaits are unknown.

The episodic nature of locomotion indicates that the initiating signals may be complemented by stop commands to allow for sudden locomotor arrest. Such signals have been found in *Xenopus* tadpole, in which head contact with obstacles activates GABAergic descending pathways that immediately terminate swimming. Likewise, in decerebrate cats, tonic electrical stimulation of the medullary and caudal pontine reticular formation leads to a general motor inhibition. Studies in mice have identified a restricted contingent of V2a neurons in the reticular formation that mediate an immediate arrest of ongoing locomotor activity. Such “V2a stop neurons” send a behaviorally relevant stop signal via descending projections to inhibitory interneurons in the ventral lumbar spinal cord that inhibits rhythm generation. A similar stop signal arrests swimming in the lamprey.

The Brain Stem Nuclei Regulate Posture During Locomotion

An important aspect of locomotor control is the regulation of posture. This general term encompasses several types of behavior, including the production of the postural support on which locomotion is superimposed, the control of balance, the regulation of interlimb coordination in quadrupeds, and the modification of muscle tonus required to adapt to locomotion on slopes or during turning. In addition, anticipatory changes in posture precede changes in voluntary gait modifications, and compensatory changes in posture follow unexpected perturbations. These functions are largely subserved by two descending systems originating from the brain stem: the vestibulospinal tract (VST), originating in the lateral vestibular nucleus (LVN), and the reticulospinal tract (RST), originating in the pontomedullary reticular formation (PMRF). Both pathways are phylogenetically old and found in all vertebrates.

Lesions of the LVN, the PMRF, or their descending axons in the spinal cord lead to a loss of weight support and the control of equilibrium, expressed as a crouched gait and swaying of the hindquarters to one side or the other. Lesions of these nuclei are also followed by large changes in the interlimb coordination between the fore- and hindlimbs. Likewise, tonic electrical or chemical stimulation of the pons and the medulla modulates the level of muscle tonus in the limbs and can either facilitate or suppress locomotion depending on the exact site stimulated (Figure 33–12).

Figure 33–12

Locomotor activity is modified by the level of postural tone. (Adapted, with permission, from Takakusaki et al. 2016.)

A. Transverse sections of the brain stem of the cat at three different rostrocaudal levels. Colored areas indicate the regions stimulated during the trials shown in part **B**. (Abbreviations: **CNF**, cuneiform nucleus; **IC**, inferior colliculus; **MLR**, mesencephalic locomotor region; **NRPo**, nucleus reticularis pontis oralis; **NRGc**, nucleus reticularis gigantocellularis; **NRMc**, nucleus reticularis magnocellularis; **PPN**, pedunculopontine nucleus.)

B. Effects of stimulating the different regions of the brain stem indicated in part **A** in the decerebrate cat.

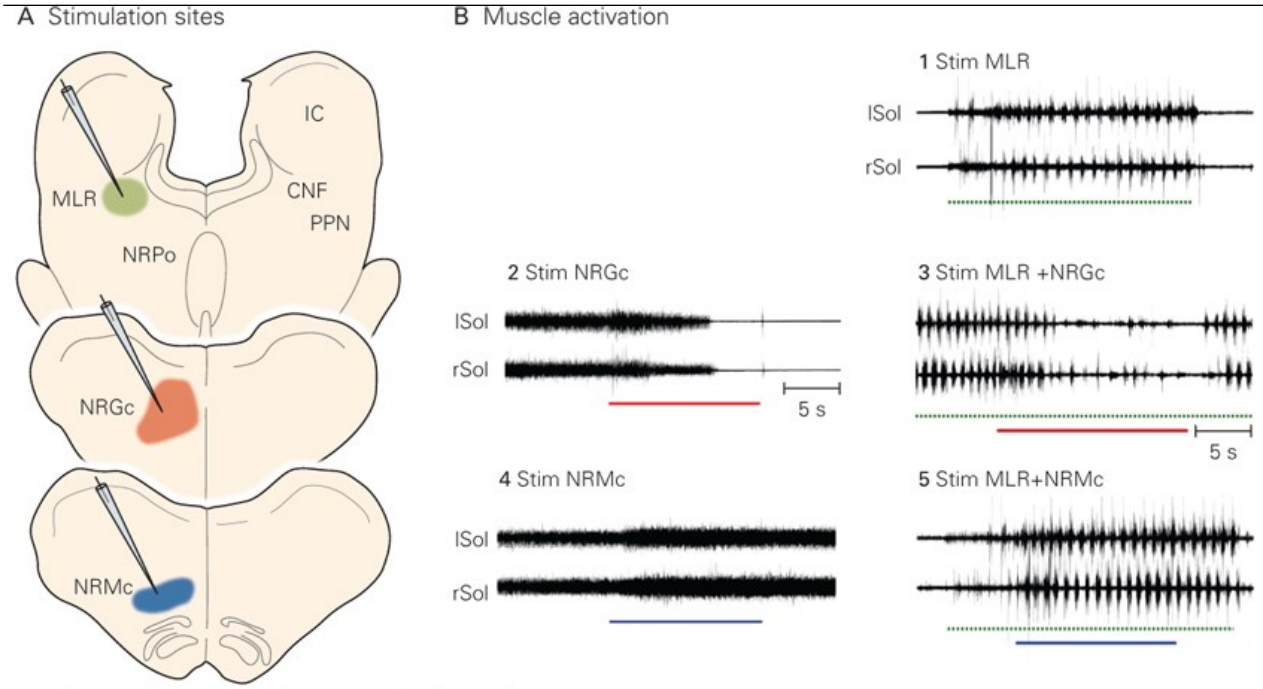
1. Stimulation of the MLR (CNF/PPN) (**green bar**) produces rhythmic activation in the left and right hindlimb extensor soleus muscles (**Sol**).

2. Tonic stimulation of the NRGc (**red bar**) in the medulla results in a loss of muscle tone in the extensor muscles.

3. Stimulation of the NRGc during CNF-induced locomotion reduces muscle tone and thereby inhibits locomotion.

4. Tonic stimulation of the NRMc (**blue bar**) in the ventral medulla produces an increase in muscle tone.

5. Stimulation of the NRMc during MLR stimulation results in increased vigor of locomotion.



Activity in the VST and RST, together with activity in the rubrospinal tract, which originates from the red nucleus, also phasically modifies the level of muscle tonus during each step. Weak electrical stimulation of any of these three structures produces phase-dependent modulation of locomotor activity. Brief activation of these pathways with short trains of stimuli produces transient changes in the amplitude of the muscle bursts but rarely produces any changes in the timing of the step cycle. Activation of the LVN primarily enhances responses in ipsilateral extensor muscles during their natural period of activity in the stance phase. In contrast, stimulation of the red nucleus generally produces transient increases in activity in contralateral flexor muscles, again during their natural period of activity in the swing phase.

Stimulation of the PMRF produces more complex and widespread responses that may modify activity in flexor muscles during the swing phase and in extensor muscles during the stance phase across all four limbs in a coordinated pattern (Figure 33–13). In flexor muscles, activity is generally facilitated by PMRF stimulation, but in extensor muscles, it may be facilitated or suppressed depending on the exact site stimulated. This phase-dependent nature of the responses is thought to be mediated by activation of interneurons in the spinal CPG. Stimulation of these three structures at higher strengths, or with longer trains, may produce changes in the timing of the step cycle as well as in the magnitude of EMG activity.

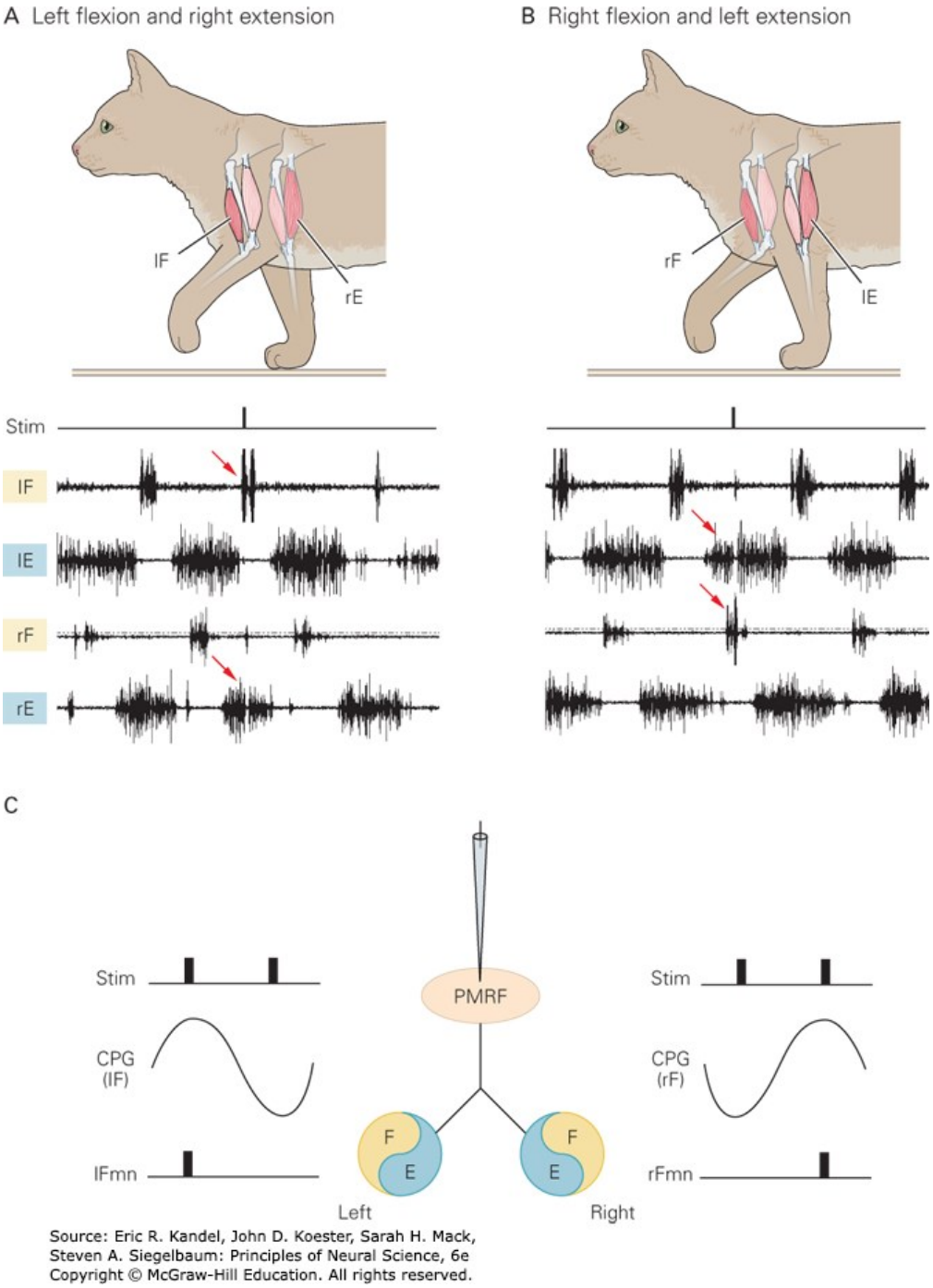
Figure 33–13

Microstimulation of the pontomedullary reticular formation (PMRF) produces phase-dependent responses in flexor and extensor muscles. (Data from T. Drew.)

A. Stimulation of the left PMRF during the swing phase of the left limb produces a transient increase in the electromyogram activity of the left flexor muscles (**lF**) and a simultaneous decrease in activity in the right extensor muscles (**rE**) (**red arrows**). There is little stimulus-evoked activity in the left extensor (**lE**) or right flexor (**rF**) muscles, which are inactive at this phase of the step cycle.

B. Stimulation at the same location in the PMRF during the swing phase of the right limb produces the inverse responses.

C. The phase-dependent nature of the responses is likely determined by the cyclical nature of the level of excitability in interneurons that are part of the locomotor central pattern generator (**CPG**). Responses are gated by activity in the flexor (**F**) and extensor (**E**) parts of the locomotor CPG. When the first stimulation arrives, flexor interneurons in the left CPG (**lF**) are active, whereas those in the right CPG (**rF**) are inactive. The stimulation therefore produces a response only in the left flexor motor neurons (**lFmn**). When the second stimulation arrives, flexor interneurons in the right CPG (**rF**) are active, whereas those on the left side are inactive, and therefore, the stimulation elicits a response only in the flexor motor neurons on the right (**rFmn**).



Source: Eric R. Kandel, John D. Koester, Sarah H. Mack, Steven A. Siegelbaum: Principles of Neural Science, 6e

During locomotion, neurons within the LVN, PMRF, and red nucleus are phasically modulated at the frequency of the step cycle. Neurons in the LVN are generally activated in phase with ipsilateral extensor muscles, whereas neurons in the red nucleus are generally active during the contralateral swing phase. Neurons in the PMRF have more complicated periods of activity and may discharge in relation to ipsilateral or contralateral flexor or extensor muscles.

Brain stem structures also contribute to more complex activities during locomotion. For example, the red nucleus contributes to the complex modifications in muscle activity required for precise modifications of gait (see below). In a complementary manner, the widespread effects of the PMRF on multiple limbs allow it to produce the coordinated changes in postural activity that accompany gait modifications. The coordination between gait modifications and postural activity is assured by the strong connections from the motor cortex to the PMRF in the same manner as for discrete voluntary movements (Chapter 34). The PMRF also contributes to the compensatory changes in posture that occur as a consequence of perturbations.

In this situation, it forms part of a spino-bulbo-spinal reflex that contributes to the widespread postural responses that follow the immediate spinal reflexes activated by a sudden perturbation.

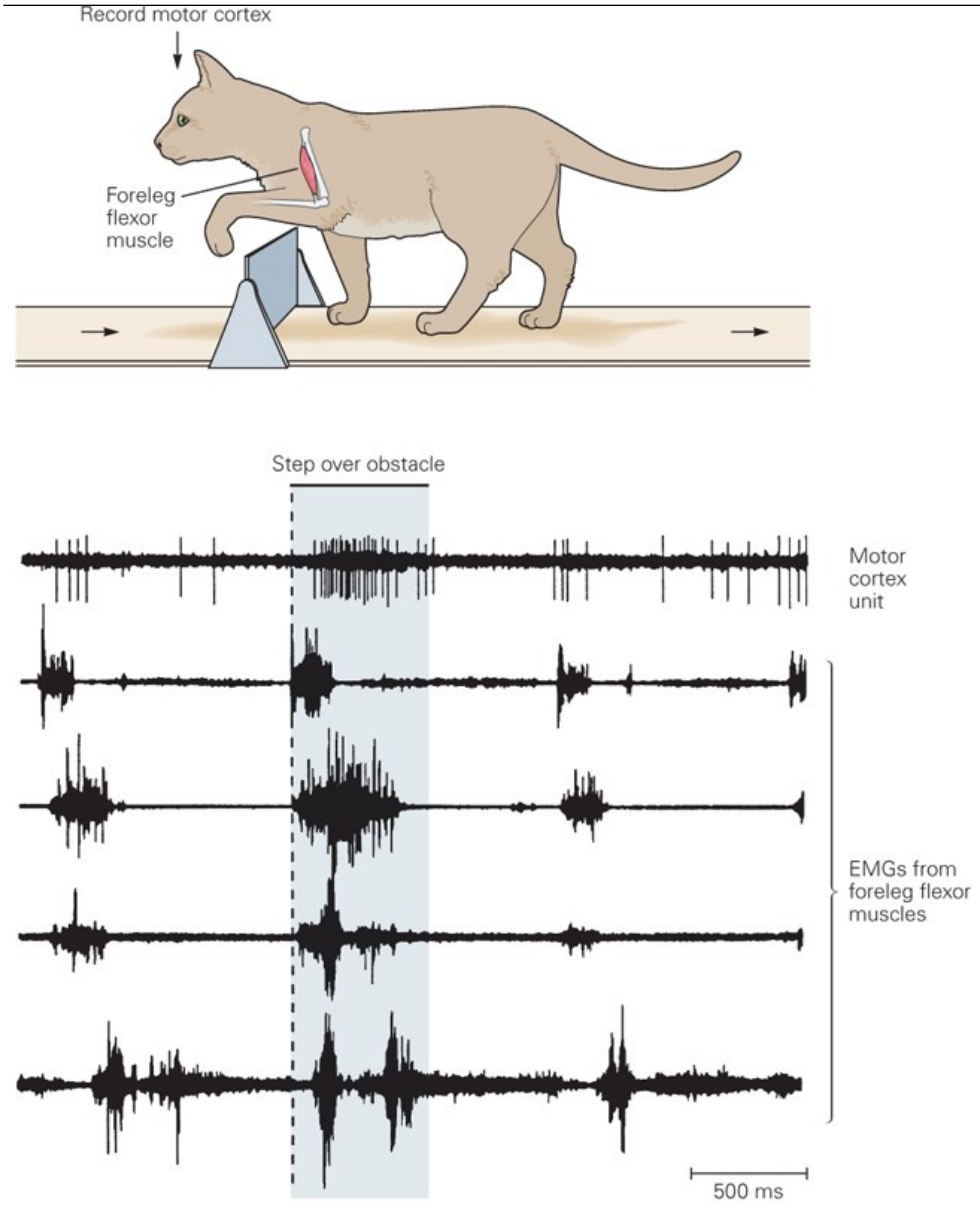
Visually Guided Locomotion Involves the Motor Cortex

Walking is most often guided by vision, and the motor cortex is largely essential for visually guided movement, especially when gait must be modified to ensure precise control over limb trajectory and foot placement. In mammals, lesions of the motor cortex do not prevent animals from walking on a smooth floor, but they severely impair “precision locomotion,” which requires a high degree of visuomotor coordination, such as walking on the rungs of a horizontal ladder, stepping over a series of barriers, and stepping over single objects placed on a treadmill belt.

Experiments in intact cats trained to step over obstacles attached to a moving treadmill belt show that precision locomotion is associated with considerable modulation of the activity of numerous neurons in the motor cortex (Figure 33–14). Other neurons in the motor cortex show a more discrete pattern of activity and are activated sequentially during different parts of the swing phase. The activity of these cortical neurons correlates with the periods of modified muscle activity required to produce the gait modifications in a similar manner to what occurs during reaching (see Figure 34–21). Such subpopulations of neurons may serve to modify the activity of the groups of synergistic muscles required to produce flexible changes in limb trajectory.

Figure 33–14

Stepping movements are adapted by the motor cortex in response to visual inputs. When a cat steps over a visible object fixed to a treadmill, neurons in the motor cortex increase in activity. This increase in cortical activity is associated with enhanced activity in foreleg muscles, as seen in the electromyograms (**EMG**). (Adapted, with permission, from Drew 1988.)



Source: Eric R. Kandel, John D. Koester, Sarah H. Mack, Steven A. Siegelbaum: Principles of Neural Science, 6e

Many of these cortical neurons project directly to the spinal cord (corticospinal neurons) and thus may regulate the activity of spinal interneurons, including those within the CPG, thereby adapting the timing and magnitude of motor activity to a specific locomotor task. Brief trains of electrical stimulation applied to either the motor cortex or the corticospinal tract in normal walking cats produce transient responses in the contralateral limb in a phase-dependent manner, similar to that produced by activity in various brain stem structures. However, in contrast to the situation observed with brain stem structures, increasing the duration of the stimulation train applied to the motor cortex frequently results in a reset of the locomotor rhythm, characterized as an interruption of the ongoing step cycle and the initiation of a new step cycle. This suggests that in mammals the corticospinal tract has privileged access to the rhythm generator of the CPG.

Planning of Locomotion Involves the Posterior Parietal Cortex

When humans and animals approach an obstacle in their pathway, they must adjust their walking pattern to move around the obstacle or step over it. Planning of these adjustments begins two or three steps before the obstacle is reached. Recent experiments suggest that the posterior parietal cortex (PPC) is particularly involved in planning gait modifications. Lesions in this region cause walking cats to misplace the positioning of their paws as they approach an obstacle and increase the probability that one or more legs contact the obstacle as they step over it.

In contrast to what is observed in the motor cortex, recordings in PPC show that many neurons increase their activity in advance of the step over the obstacle. Moreover, many cells in the PPC discharge similarly regardless of which leg is first to step over the obstacle (Figure 33–15A,B). Such cells may provide an estimation of the position of the body with respect to objects in the environment (Figure 33–15B), allowing animals to modify gait as they approach the obstacle. The manner in which the PPC interacts with other cortical and subcortical structures generally considered to be involved in motor planning is unknown. However, recent work shows that the premotor cortex also makes an important contribution to planning visually guided gait modifications (Figure 33–15C) and may be implicated in the transformation of a global signal providing information concerning obstacle location to the muscle-based signal necessary for the execution of the step over the obstacle.

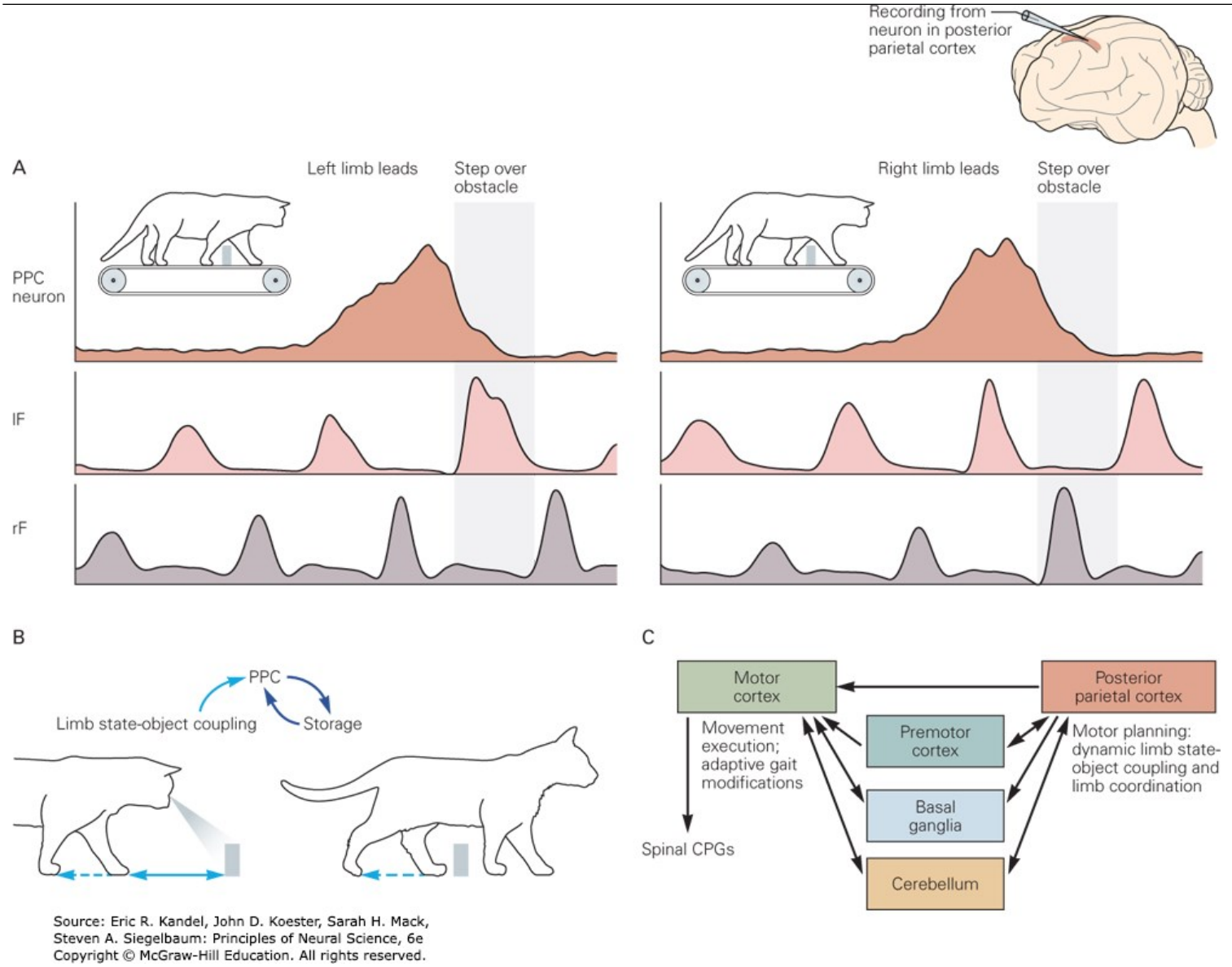
Figure 33–15

Neurons in the posterior parietal cortex (PPC) are involved in planning voluntary gait modifications.

A. Activity of a PPC neuron in the right cortex during a step over the obstacle when the left or right forelimb is the first to step over the obstacle. In each situation, the cell in the PPC discharges two to three steps in advance of the step over the obstacle.

B. The observation that PPC neurons discharge independent of which limb is the first to step over the obstacle suggests a global function of PPC in the planning of locomotion. In a general scheme, the PPC neurons are involved in the estimation of the relative location of an object with respect to the body (limb state–object coupling [**double arrow**]) and storage information in the PPC for later retrieval.

C. The PPC does not act alone in planning gait modifications. It is part of a cortical and subcortical network that includes, among other structures, the premotor cortex, the basal ganglia, and the cerebellum. Connections exist between each of these structures as well as between each of them and the motor cortex, which is responsible for the execution of the gait modification. (Abbreviation: **CPG**, central pattern generator.) (Adapted, with permission, from Drew and Marigold 2015.)



Visual information about the size and location of an obstacle is also stored in working memory, a form of short-term memory (Chapter 52). This information is used to ensure that gait modifications in the hindlimb are coordinated with those of the forelimb and is necessary because the obstacle is no longer within the visual field by the time the hindlimbs are stepping over it. The neurobiological mechanisms underlying this form of working memory remain to be established, but the persistence of the memory appears to depend, at least in part, on neuronal systems in the PPC. With bilateral lesions or cooling of the medial PPC, the memory is completely abolished (Figure 33–16A). Complementing this observation is the finding that the activity of some neurons in the PPC is elevated during a step over an obstacle, as well as throughout the time the animal straddles the obstacle (Figure 33–16B). This activity could represent the working memory of key features of the obstacle such as height.

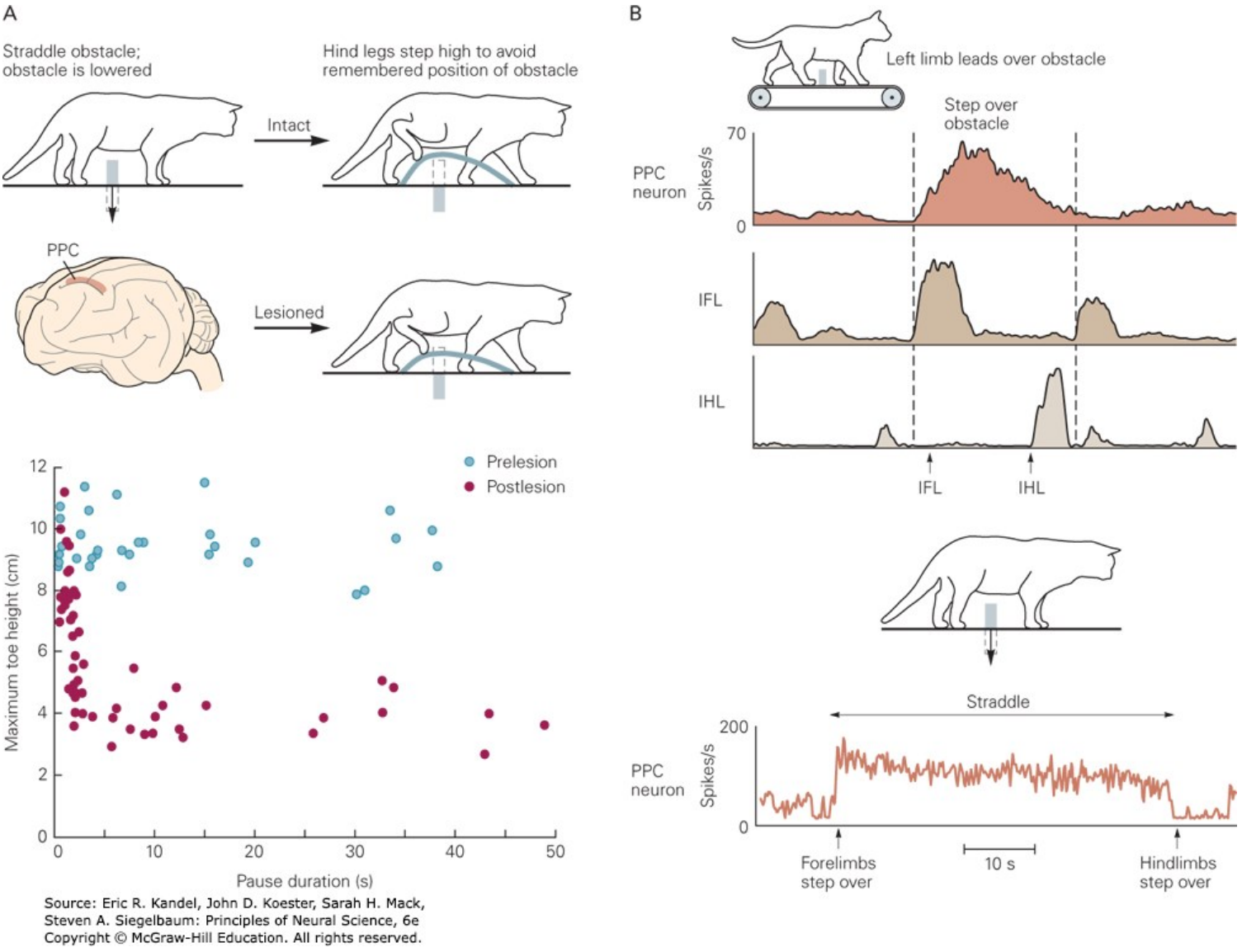
Figure 33–16

The posterior parietal cortex (PPC) is involved in maintaining an estimate of an obstacle in working memory during locomotion.

A. Upper figure: Normal animals were trained to walk forward, step over an obstacle, and then pause. While the animal paused, the obstacle was removed. When walking resumed, the hind legs stepped high to avoid the remembered obstacle. This memory lasted for more than 30 seconds. The trajectory of the hindlimbs was scaled appropriately for the height of the obstacle and for the relative position of the hind paws. Bilateral lesions of the PPC led to an impairment in the memory, making it impossible for the animal to pass the obstacle without hitting it. **Lower figure:** Following the lesion, animals stored the memory for only 1 to 2 seconds, and the maximum height of the toe was insufficient to clear the obstacle and was

significantly lower than in the prelesion condition. (Adapted from McVea and Pearson 2009.)

B. Upper figure: Neurons recorded in an intact animal in the PPC on the right side discharged in the period between the passage of the left forelimb (**lFL**) and hindlimb (**lHL**) over an obstacle (represented by electromyogram activity from representative flexor muscles in each limb). This discharge may be used to coordinate the movement of the hindlimb with that of the forelimb during the visually guided gait modification. **Lower figure:** When the cat steps over an obstacle and pauses, as in part **A**, cells in the PPC show a maintained discharge that could provide the neural representation of the working memory. (Adapted, with permission, from Lajoie et al. 2010.)



The Cerebellum Regulates the Timing and Intensity of Descending Signals

Damage to the cerebellum results in marked abnormalities in locomotor movements, including the need for a widened base of support, impaired coordination of joints, and abnormal coupling between limbs during stepping. These symptoms, which are characteristic of *ataxia* (Chapter 37), indicate that the cerebellum contributes importantly to the regulation of locomotion.

A major function of the cerebellum is to correct movement based on a comparison of the motor signals sent to the spinal cord and the movement produced by that motor command (Chapter 37). In the context of locomotion, the motor signal is generated by neurons in the motor cortex and brain stem nuclei. Information about the movement comes from the ascending spinocerebellar pathways. For the hind legs of the cat, these are the dorsal

and ventral spinocerebellar tracts. Neurons in the dorsal spinocerebellar tract (DSCT neurons) are strongly activated by numerous leg proprioceptors and thus provide the cerebellum with detailed information about the mechanical state of the hind legs. In contrast, neurons in the ventral tract (VSCT neurons) are activated primarily by interneurons in the CPG, thus providing the cerebellum with information about the state of the spinal locomotor network.

During locomotion, the motor command (the central efference copy), the movement (the afference copy, via the DSCT), and the state of the spinal networks (the spinal efference copy, via the VSCT) are integrated within the cerebellum and expressed as changes in the pattern of rhythmical discharge of Purkinje cells in the cerebellar cortex and neurons in the deep cerebellar nuclei. These signals from the deep cerebellar nuclei are then sent to the motor cortex and the various brain stem nuclei where they modulate descending signals to the spinal cord to correct any motor errors.

Behavioral experiments show that the cerebellum also plays an important role in the adaptation of gait. For example, when subjects walk on a split treadmill, so that each leg walks at a different speed, they initially show a very asymmetric gait before adapting over time to a more asymmetric one. When the two treadmill belts are reset to the same speed, they again show an asymmetric gait, demonstrating that the experimental condition had produced adaptation (see Figure 30–13). Patients with damage to the cerebellum are not able to adapt to this condition.

The Basal Ganglia Modify Cortical and Brain Stem Circuits

The basal ganglia are found in all vertebrates from the oldest vertebrates to primates and probably contribute to the selection of different motor patterns. The importance of the basal ganglia to the control of locomotion is clearly demonstrated by the deficits in locomotion observed in patients with Parkinson disease, which disrupts the normal functioning of the basal ganglia due to degradation of their dopaminergic inputs from the substantia nigra (Chapter 38).

Such patients show a characteristic slow, shuffling gait and, in later stages of the disease, can also show “freezing” of gait. Patients with Parkinson disease also show problems with balance during locomotion and with the anticipatory postural adjustments that occur at the initiation of a gait pattern. These deficits suggest that the basal ganglia contribute to the initiation, regulation, and modification of gait patterns. This regulation is mediated by the two major projections of the basal ganglia to the brain stem pathways and cortical structures.

The basal ganglia influence brain stem activity through their projections to the PPN. The PPN receives inhibitory inputs from GABAergic inhibitory neurons in the substantia nigra pars reticulata (SNr) as well as from the globus pallidus pars interna (GPi); it also receives glutamatergic input from neurons in the subthalamic nucleus (STN). Decreased inhibitory input and increased glutamatergic input to PPN from the basal ganglia are thought to promote activity in PPN and favor exploratory locomotion. The STN and GPi are major targets of deep brain stimulation for improvement of motor symptoms such as rigidity and reduced mobility in patients with Parkinson disease.

The basal ganglia influence cortical activity by means of its connections via the thalamus to different parts of the frontal cortex, including the supplementary motor regions. These connections allow the basal ganglia to exert a modulatory effect on visually guided locomotion, possibly by selecting the appropriate motor patterns required in different behavioral situations.

Computational Neuroscience Provides Insights Into Locomotor Circuits

While functional studies have revealed much about the organization of the locomotor networks, their overall complexity makes it difficult to capture the integrative function of synaptic and cellular properties of the circuit. Computational network modeling, however, allows one to simulate the circuit activity and to investigate the dynamic interactions between the circuit elements. Computational models can be developed at many levels: to study the ionic basis of neural activity within a given circuit, to study the connectivity between different groups of neurons in a particular circuit, or to better understand the interactions between different structures in the locomotor network. Computational models at each of these levels have been developed to study rhythm and pattern generation in both invertebrates and vertebrates and in the latter, ranging from the lamprey to mammals. As in other domains, approaches combining experimental manipulation and computational modeling are likely to increase in the coming years and have the potential to advance our understanding of the complex systems and interconnections between structures that are required to produce the full locomotor repertoire.

Neuronal Control of Human Locomotion Is Similar to That of Quadrupeds

By necessity, most of our understanding of the neural mechanisms underlying the control of locomotion comes from experiments on quadrupedal animals. Nonetheless, the available evidence suggests that all the major principles concerning the origin and regulation of walking in quadrupeds also pertain to locomotion in humans. Although the issue of whether CPGs exist in humans remains contentious, several observations are compatible with the view that CPGs are important for human locomotion.

For example, observations of some patients with spinal cord injury parallel the findings from studies of spinal cats. Striking cases of patients with nearly complete transection of the spinal cord have shown uncontrollable, spontaneous, rhythmic movements of the legs when the hips were extended. This behavior closely parallels the rhythmic stepping movements in chronic spinal cats. Moreover, tonic electrical stimulation of the spinal cord below the injury can evoke locomotor-like activity, as in other mammals.

Parallels between human and quadrupedal walking have also been found in patients trained after spinal cord injury. Daily training combined with drug treatments restores stepping in spinal cats and improves stepping in patients with chronic spinal injuries. People with severe spinal cord injury who have been exposed to both treadmill-induced stepping and drug treatments similar to those that have been shown to activate the CPG in cats have demonstrated dramatic improvements in the ability to produce locomotion (Box 33–4). These results suggest that CPGs are present in humans and share functional similarities with CPGs found in other vertebrates.

Box 33–4 Rehabilitative Training Improves Walking After Spinal Cord Injury in Humans

According to the World Health Organization, between 250,000 and 500,000 people worldwide incur spinal cords injuries annually. For many, this results in permanent loss of sensation, movement, and autonomic function. The devastating loss of functional abilities, together with the enormous cost of treatment and care, creates an urgent need for effective methods to repair the injured spinal cord and to facilitate functional recovery.

Over the past decades, progress has been made in animal research aimed at preventing secondary damage after injury, repairing the axons of lesioned neurons in the spinal cord, and promoting the regeneration of severed axons through and beyond the site of injury. In many instances, the regeneration of axons has been associated with modest recovery of locomotor function. However, none of the regeneration strategies has reached the point where they can be confidently used in humans with spinal cord injury.

Thus, rehabilitative training is the preferred treatment for people with spinal cord injury. One especially successful technique for enhancing walking in patients with partial damage to the spinal cord is repetitive, weight-supported stepping on a treadmill (Figure 33–17). This technique is based on the observation that spinal cats and rodents can be trained to step with their hind legs on a moving treadmill.

For humans, partial support of the body weight through a harness system is critical to the success of training; presumably, it facilitates the training of spinal cord circuits by reducing the requirements for supraspinal control of posture and balance.

Although the neural basis for the improvement in locomotor function with treadmill training has not been established, it is thought to depend on synaptic plasticity in local spinal circuits as well as successful transmission of at least some command signals from the brain through preserved descending pathways if the spinal cord injury is only partial.

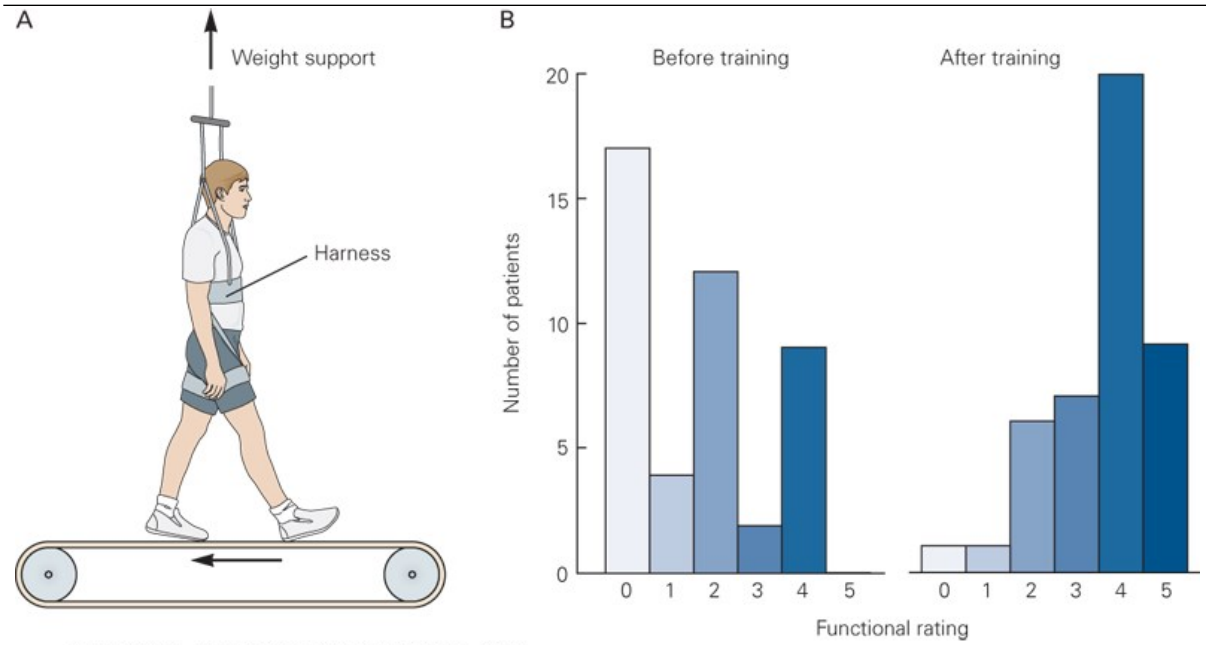
Locomotor training is sometimes combined with other treatments. These include different types of medication designed to reduce spasticity, seen as involuntary muscle contractions, and facilitation of activity in spinal circuits by electrical transcutaneous activation of spinal circuits and/or activation of corticospinal pathways by transcranial magnetic stimulation.

Figure 33–17

Treadmill training improves locomotor function in patients with partial spinal cord injury.

A. The patient is partially supported on a moving treadmill by a harness, and stepping movements are assisted by therapists.

B. Locomotor function improvement in 44 patients with chronic spinal cord injury after daily training lasting from 3 to 20 weeks. The functional rating ranges from 0 (unable to stand or walk) to 5 (walking without devices for more than five steps). (Adapted, with permission, from Wernig et al. 1995. Copyright © 2006, John Wiley and Sons.)



Source: Eric R. Kandel, John D. Koester, Sarah H. Mack, Steven A. Siegelbaum: Principles of Neural Science, 6e

Compelling evidence for the existence of spinal CPGs in humans also comes from studies in human infants who make rhythmic stepping movements immediately after birth if held upright and moved over a horizontal surface. This strongly suggests that some of the basic neuronal circuits for locomotion are innate and present at birth when descending control systems are not well developed. Because stepping can also occur in infants who lack cerebral hemispheres (*anencephaly*), these circuits must be located at or below the brain stem, perhaps entirely within the spinal cord.

During the first year of life, as automatic stepping is transformed into functional walking, these basic circuits are thought to be brought under supraspinal control. In particular, the stepping pattern gradually develops from a more primitive flexion-extension pattern that generates little effective forward movement to the mature pattern of complex movements. It is plausible, based on studies of cats, that this adaptation reflects maturation of descending systems that originate in the motor cortex and brain stem nuclei and are modulated by the cerebellum.

At the cortical level, stroke involving the motor cortex or damage to the corticospinal tracts leads to deficits in locomotion, as in cats. However, the deficits in humans are much stronger than in cats or even nonhuman primates, suggesting that the motor cortex in humans plays a more important role in locomotion than in other mammals. Studies using transcranial magnetic stimulation (TMS) to modulate motor cortical activity also show that the motor cortex contributes importantly to the control of human locomotion. TMS parameters that result in cortical inactivation, for example, produce a decrease in the level of muscle activity during locomotion. In contrast, TMS parameters that activate the motor cortex improve the recovery of locomotion following incomplete spinal cord injury.

Imaging studies, together with high-resolution electroencephalogram recordings, show changes in the activity of several cortical regions, including the motor cortex, premotor cortex, and PPC, during locomotion and particularly during imagined locomotion over obstacles. Imaging studies have also shown increased activity during locomotion in those parts of the midbrain shown to be important for the initiation and speed control of locomotion in animals. Similarly, neurons in the pedunculopontine nucleus can be affected in Parkinson disease, contributing to the severe gait disturbances seen in the late phase of the disease.

Highlights

1. Locomotion is a highly conserved behavior that is essential for the survival of the species. Our understanding of the neuronal mechanisms involved in the generation and control of locomotion came initially from the study of phylogenetically older animals, such as the lamprey and the tadpole. More recently, in mammals, with their more complex nervous systems, the organization of the different neural pathways involved in the generation and regulation of locomotion has also been determined in significant detail.

2. The spinal cord, in isolation from descending and rhythmical peripheral afferent inputs, can generate a complex locomotor pattern that contains

elements of the rhythms and patterns observed in intact animals. The circuits responsible for producing this activity are referred to as central pattern generators (CPGs). Activity in spinal circuits can be modified by experience.

3. The basic components of CPGs controlling swimming are excitatory rhythm-generating neurons together with commissural inhibitory neurons responsible for left–right alternation. This organizational principle is also found in CPGs controlling limbed movements with the addition of flexor-extensor pattern-generating circuits and additional commissural neuronal networks. The circuits in the locomotor networks have a modular organization with distinct transmitter and molecular codes for the constituent neurons. Descending command signals act on these circuit elements to produce the diverse aspects of locomotor behavior.

4. Ionic membrane properties in interneurons and motor neurons contribute to rhythm and pattern generation. Cell-specific manipulation of these properties will enable a precise understanding of their relative contributions to locomotor production.

5. Peripheral afferent inputs modulate the function of spinal locomotor circuits. Proprioceptive sensors are used to stabilize phase transitions between stance and swing (and vice versa), whereas input from exteroceptors is used to modify limb activity in response to unexpected perturbations.

6. Circuits that are involved in initiating locomotion, controlling speed of locomotion, and selecting gaits are localized in the midbrain and encompass excitatory neurons in the pedunculopontine and cuneiform nuclei. These excitatory nuclei serve diverse roles in controlling either slow explorative locomotion or the full range of speeds and gaits including fast escape locomotion. Molecular-genetically driven cell-specific approaches allow unparalleled access to the organization of these pathways in the brain stem and how they integrate with spinal locomotor networks.

7. Activity in the three main structures in the brain stem with axons that descend to the spinal cord (the pontomedullary reticular formation, the lateral vestibular nucleus, and the red nucleus) contributes to the control of posture and interlimb coordination. Signals from these structures modify the level of muscle activity in a structure-specific manner.

8. The motor cortex provides precise control of muscle activity patterns to allow animals to make visually guided anticipatory adjustments of their gait. The signal from the motor cortex is integrated into the ongoing rhythm.

9. The posterior parietal cortex (PPC) is part of a network that contributes to the advanced planning of gait based on visual information. PPC neurons estimate the relative location of objects with respect to the body and retain information in working memory to facilitate coordination of the limbs. The contribution of other cortical and subcortical areas to locomotor planning remains little studied.

10. Inputs from the cerebellum and the basal ganglia are used to correct motor errors and select the appropriate patterns of motor activity. The contribution of the basal ganglia to the control of locomotion is complex and is only now being determined.

11. The available evidence suggests that the neural control mechanisms determined from experiments in animals are also used to control locomotion in humans, including the existence of a CPG. Major advances remain to be made in understanding the mechanisms of spinal and supraspinal influences on human locomotor control.

12. Recent technological advances now give us an unparalleled opportunity to investigate the control mechanisms underlying locomotion. Molecular and genetic advances provide the ability to manipulate behavior at both the cellular and systems level and allow detailed study of the contributions of brain stem and spinal circuits to the initiation and regulation of locomotion. Advances in multineuronal recording techniques in animals, as well as the development of high-resolution recordings of human brain activity, will facilitate our understanding of the contribution of cortical structures to the control of locomotion.

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