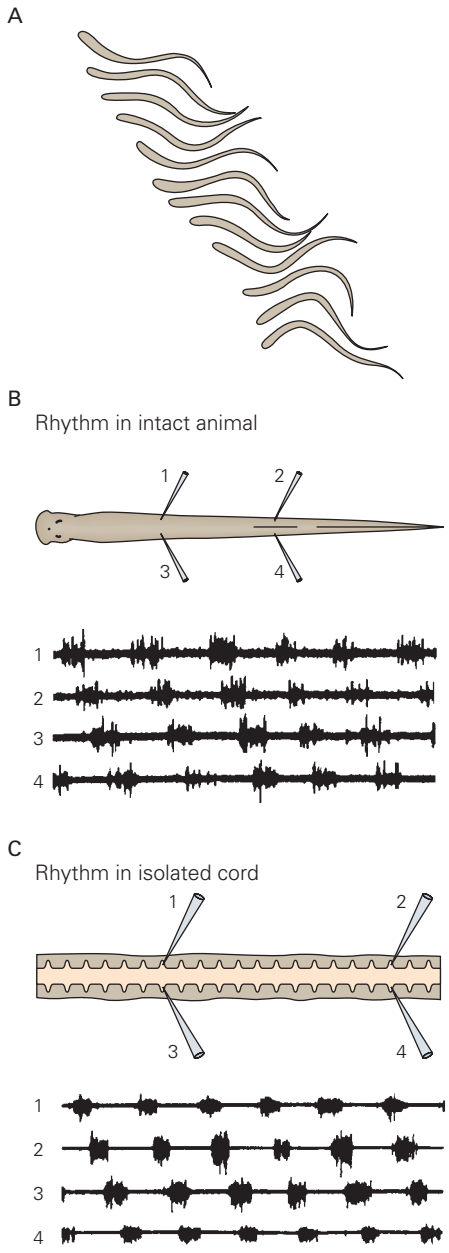


Figure 33–3 Lamprey swimming. The lamprey swims by means of a wave of muscle contractions traveling down one side of the body 180° out of phase with a similar traveling wave on the opposite side (**A**). This pattern is evident in electromyogram recordings from four locations along the animal during normal swimming (**B**). A similar pattern is recorded from four ventral roots in an isolated cord (**C**). (Data from S Grillner.)

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).

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

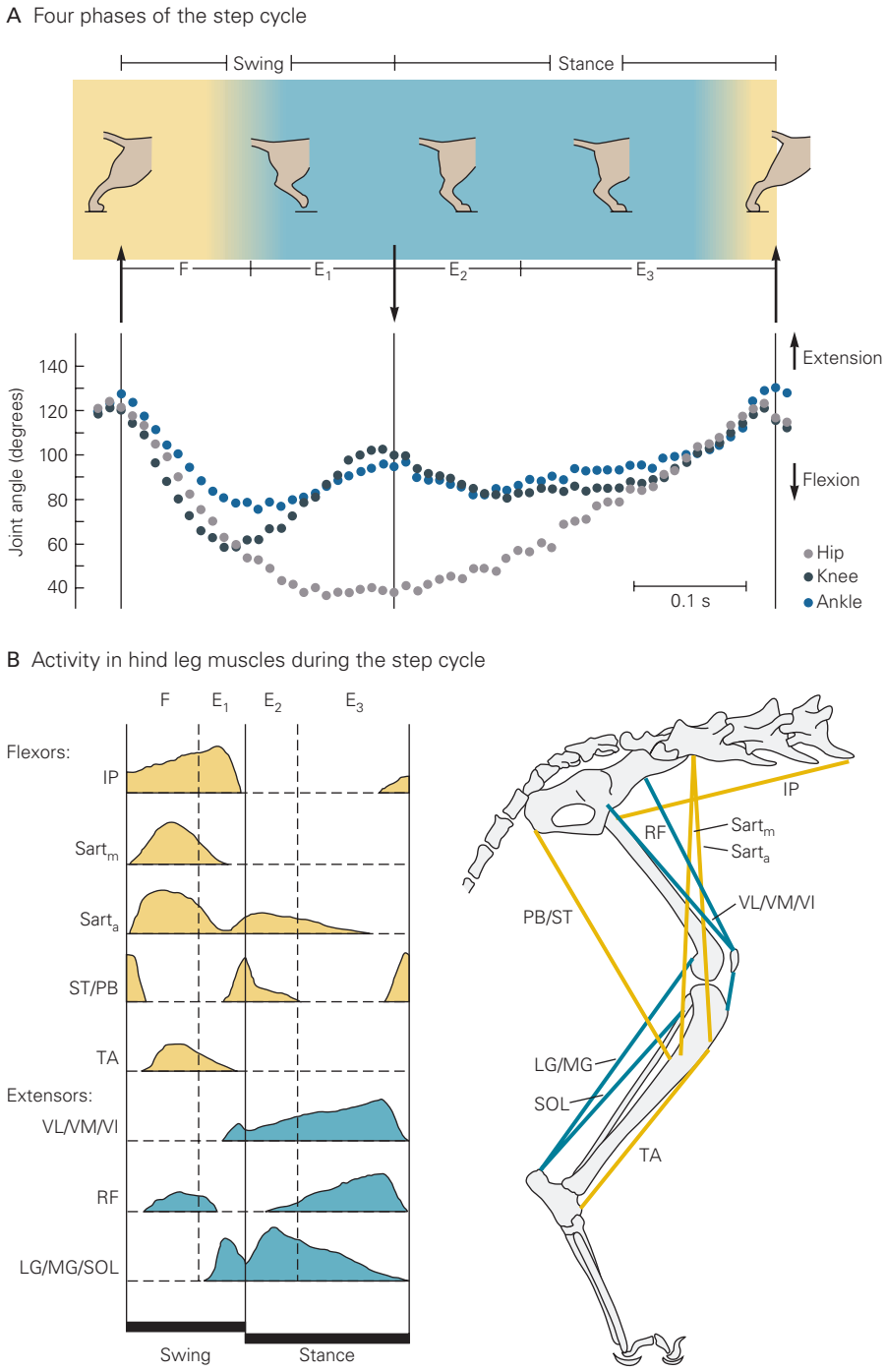


Figure 33–4 Stepping is produced by complex patterns of contractions in leg muscles.

A. The step cycle is divided into four phases. The flexion (**F**) and first extension (E_1) phases occur during the swing phase, when the foot is off the ground, whereas second extension (E_2) and third extension (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; **$Sart_m$** and **$Sart_a$**, medial and anterior sartorius; **SOL**, soleus; **ST**, semitendinosus; **TA**, tibialis anterior; **VL**, **VM**, and **VI**, vastus lateralis, medialis, and intermedius.)

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.

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

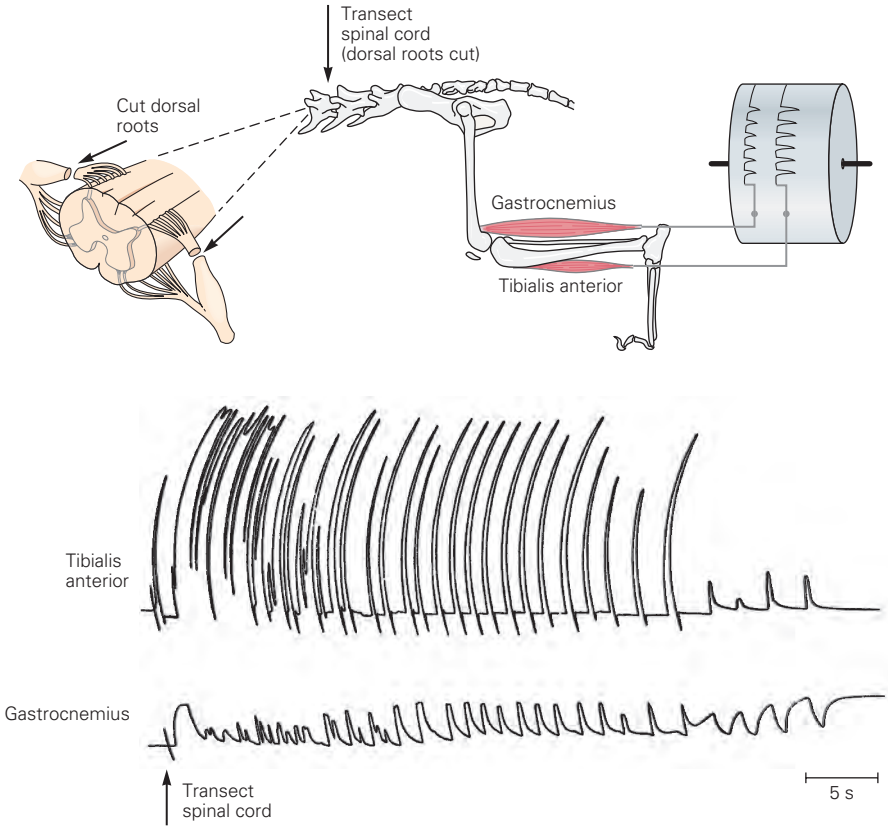


Figure 33–5 Rhythmic stepping is generated by spinal networks. The existence of intrinsic spinal networks was first demonstrated in 1911 by Thomas Graham Brown who developed an experimental preparation in which the dorsal roots were cut so that sensory information from the limb could not reach the spinal 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.

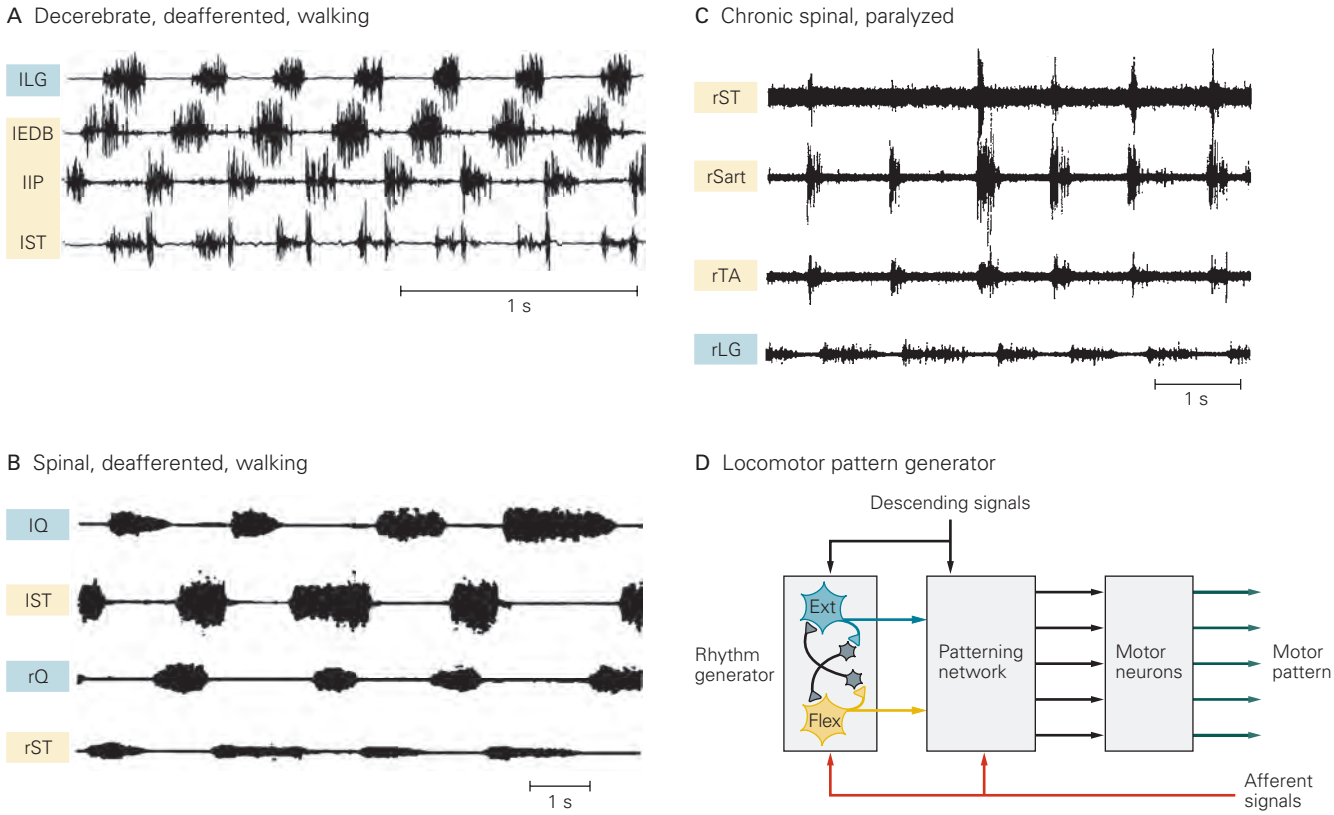


Figure 33–6 Spinal circuits generate both a rhythm and a pattern.

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.)

the spatiotemporal details of the pattern of activity observed in the intact cat (Figure 33–6C).

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).

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.

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).

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.

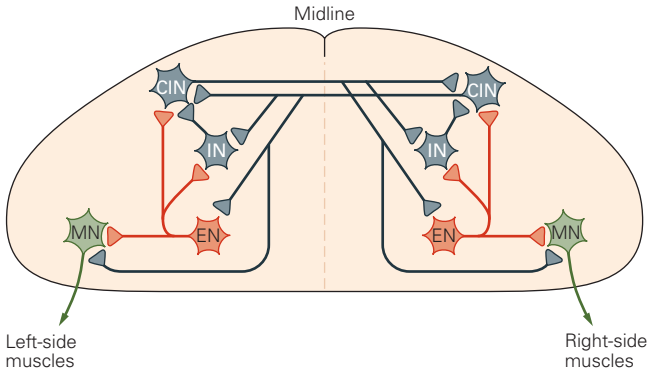
Left–Right Coordination

Left–right alternation, for both swimming and overground 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).

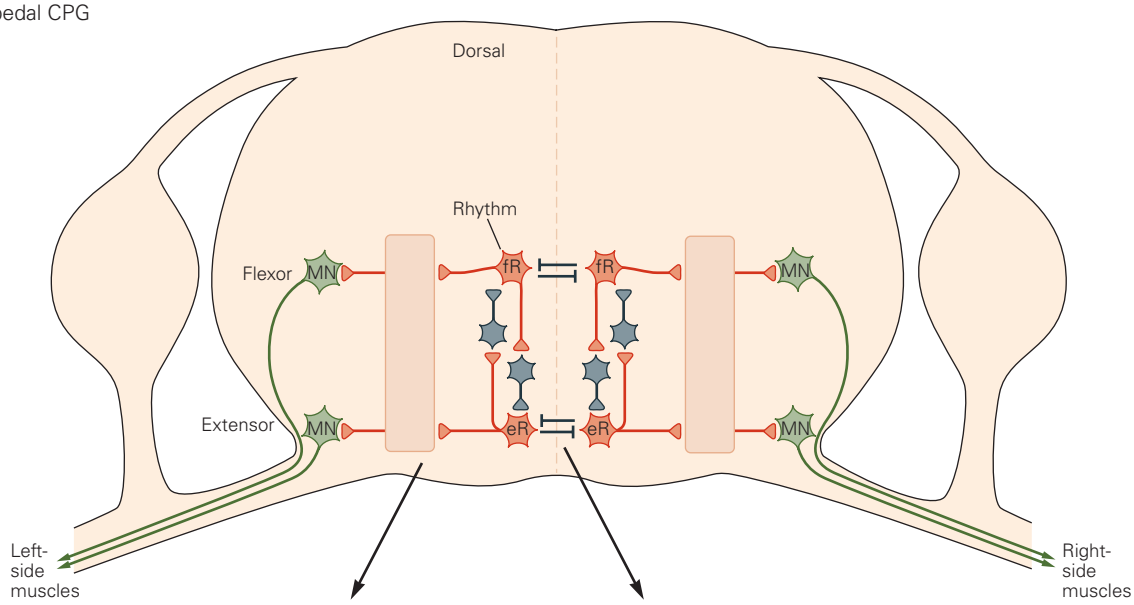
The dual-mode left–right alternating pathways are driven directly by the rhythm-generating neurons or indirectly by other non–rhythm-generating excitatory neurons, including the V2a-Shox2^{Off} neurons that are recruited at high speeds of locomotion and synaptically connect to the $V0_V$ neurons. The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

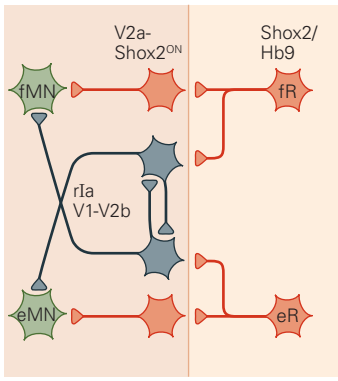
A Swimming CPG: Rhythm and left–right coordination circuits



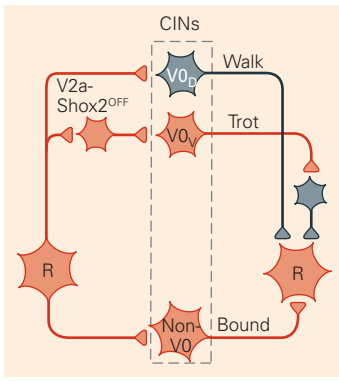
B Quadrupedal CPG



1 Flexor and extensor coordination



2 Left–right coordination



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).

Activation of sensory fibers from Golgi tendon organs and muscle spindles in ankle extensor muscles prolongs the stance phase, often delaying the onset of

Figure 33–7 (Opposite) 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.)

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.