## 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.

## 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.

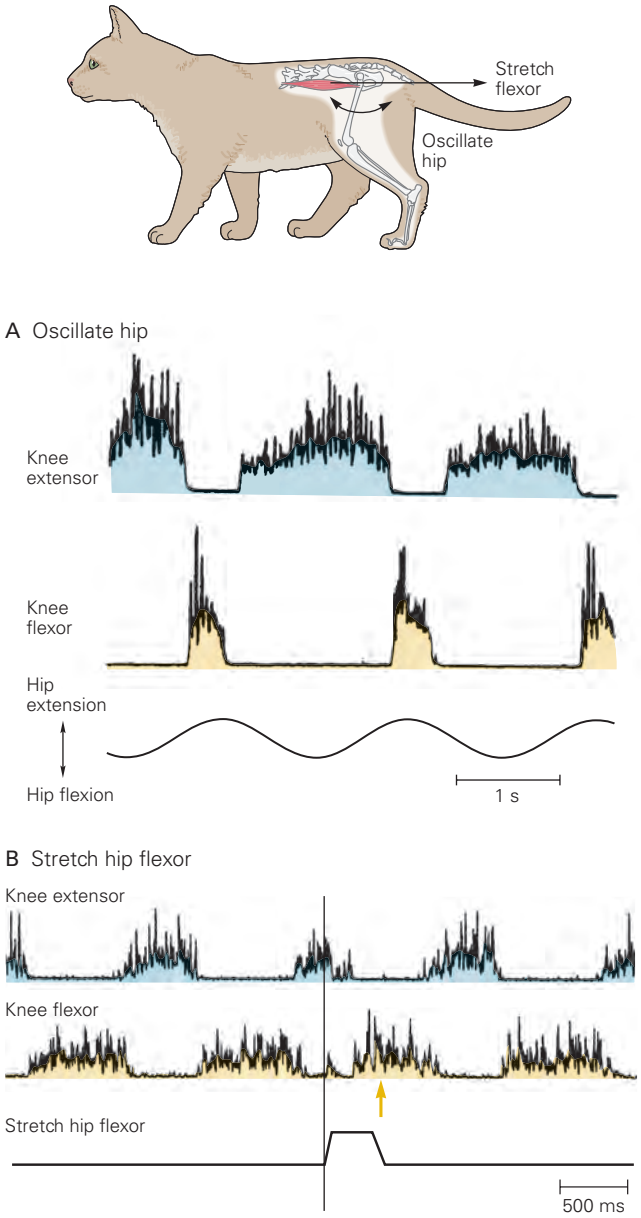


**Figure 33–8** Hip extension initiates the transition from stance to swing phase of walking.

**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.)

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.

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

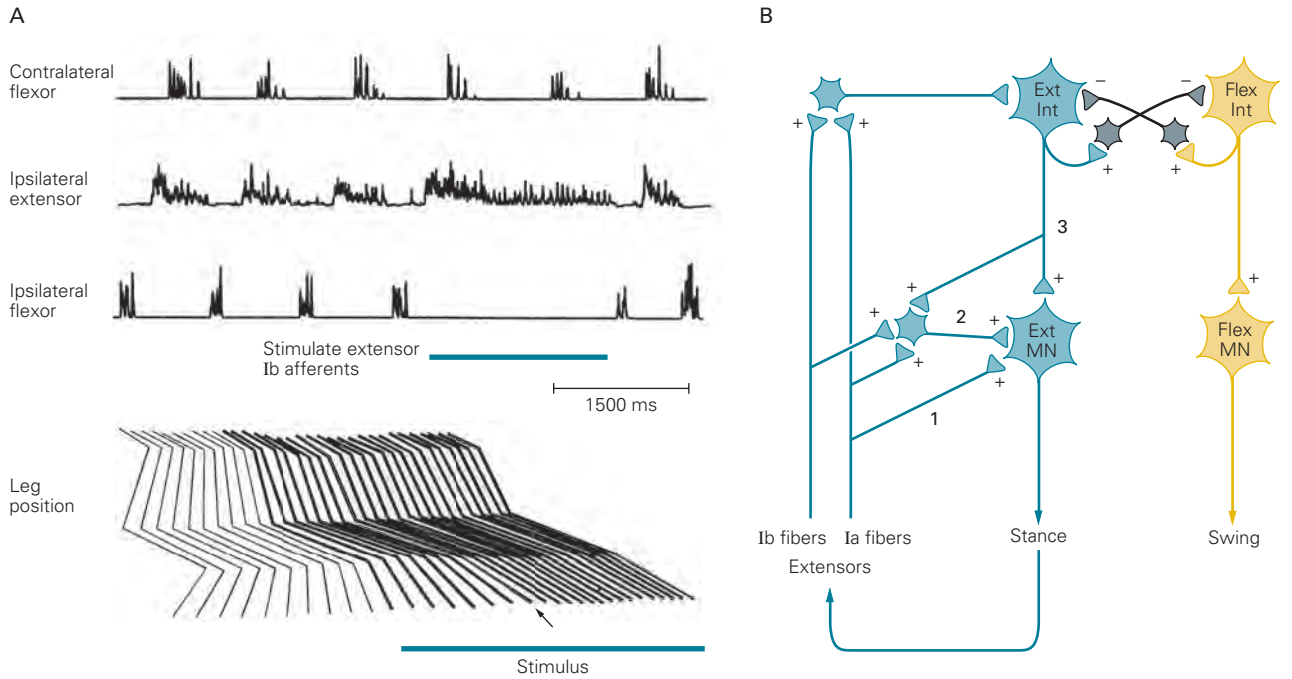


**Figure 33–9** The swing phase of walking is initiated by sensory feedback from extensor muscles.

**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.

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).

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.

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

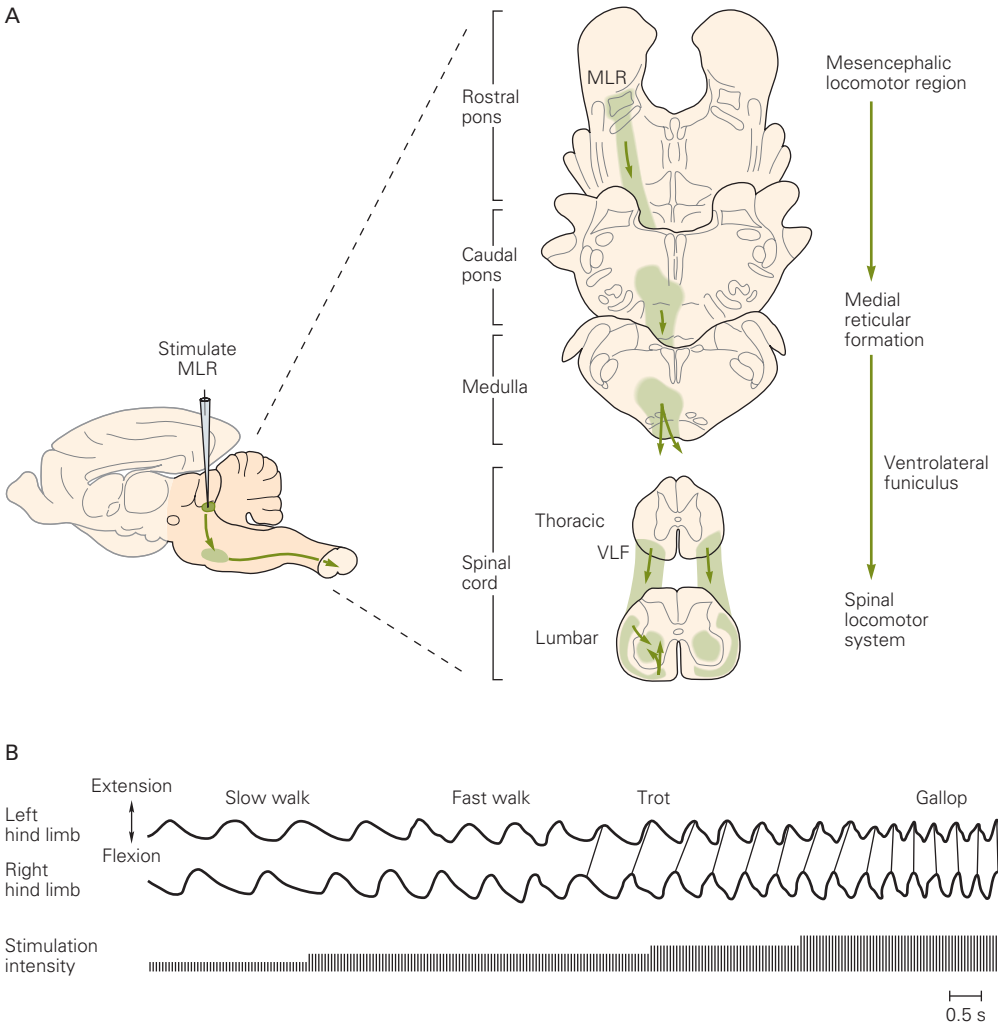


**Figure 33–10** The mesencephalic locomotor region initiates locomotion.

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.)

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

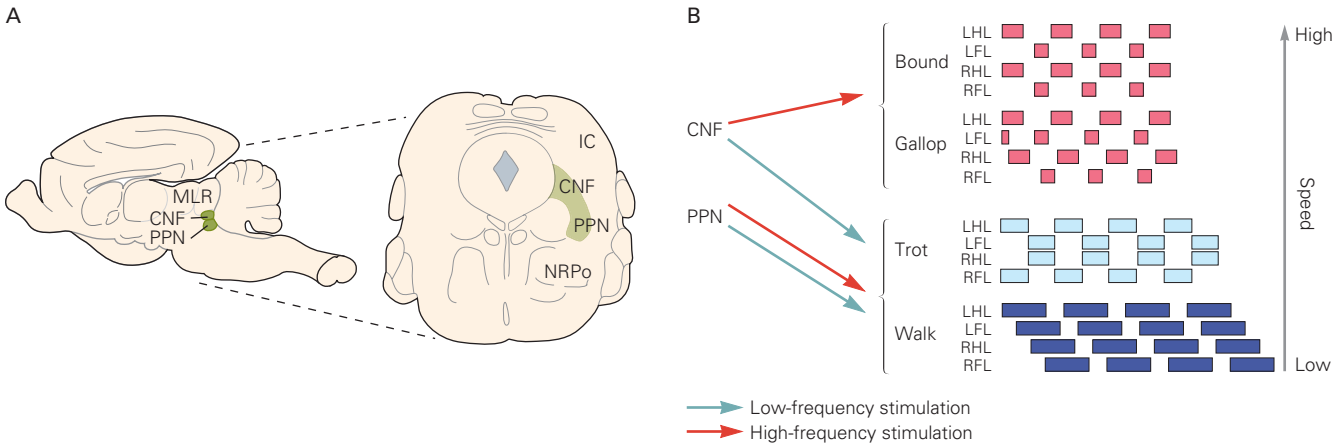


**Figure 33–11** The mesencephalic locomotor region is composed of dual midbrain glutamatergic nuclei that control initiation of locomotion, speed and gait regulation, and context-dependent selection of locomotion.

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.)

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).

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

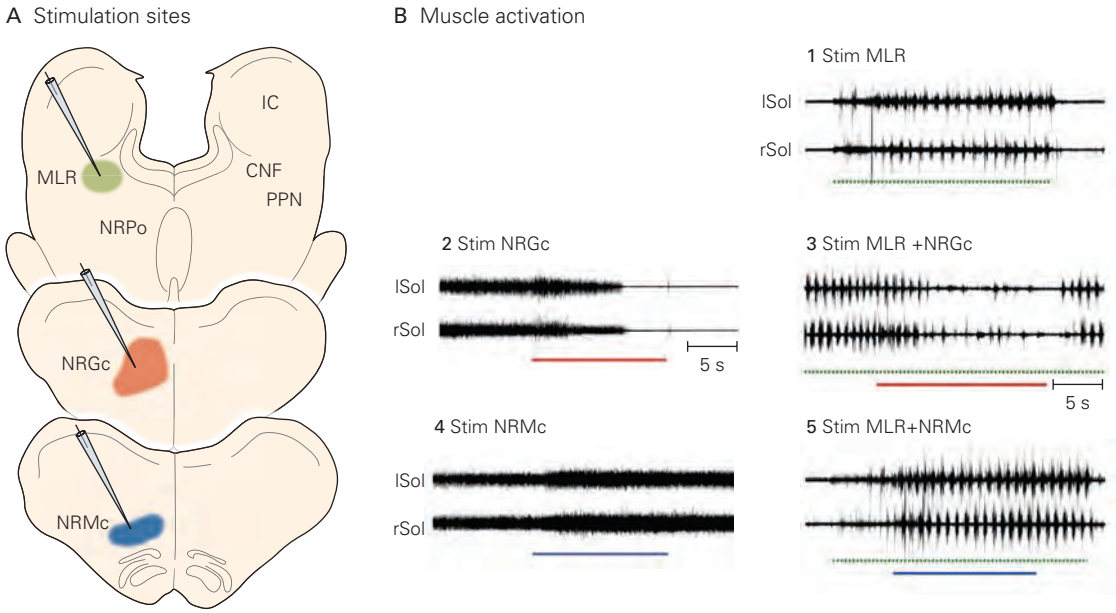


**Figure 33–12** Locomotor activity is modified by the level of postural tone. (Adapted, with permission, from Takakusaki et al. 2016.)

**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.

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.

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

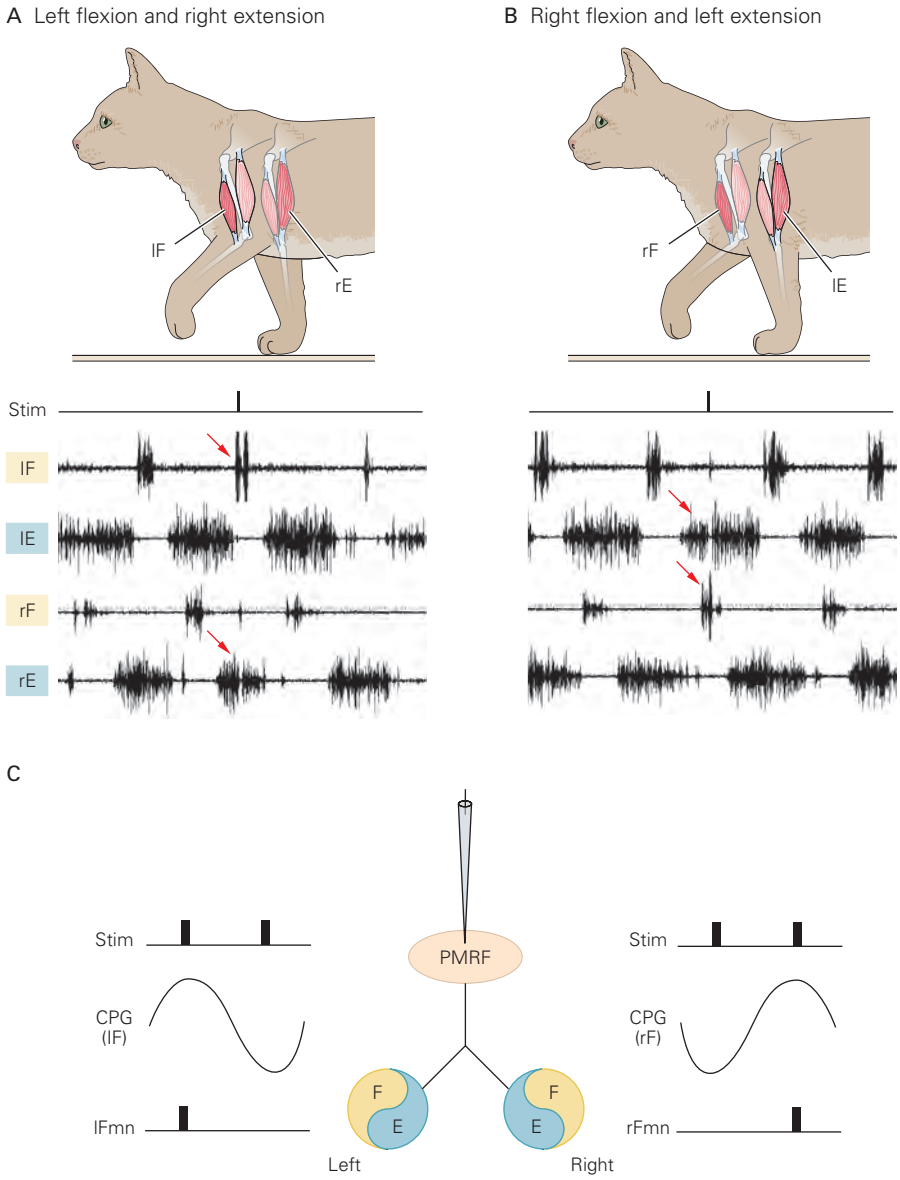


**Figure 33–13** Microstimulation of the pontomedullary reticular formation (PMRF) produces phase-dependent responses in flexor and extensor muscles. (Data from T. Drew.)

**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 (**IF**) 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**).

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