Damage to the Central Nervous System Produces Characteristic Alterations in Reflex Responses

Stretch reflexes are routinely used in clinical examinations of patients with neurological disorders. They are typically elicited by sharply tapping the tendon of a muscle with a reflex hammer. Although the responses are often called tendon reflexes or tendon jerks, the receptor that is stimulated, the muscle spindle, actually lies in the muscle rather than the tendon. Only the primary sensory fibers in the spindle participate in the tendon reflex, for these are selectively activated by a rapid stretch of the muscle produced by the tendon tap.

Measuring alterations in the strength of the stretch reflex can assist in the diagnosis of certain conditions and in localizing injury or disease in the central nervous system. Absent or hypoactive stretch reflexes often indicate a disorder of one or more of the components of the peripheral reflex pathway: sensory or motor axons, the cell bodies of motor neurons, or the muscle itself (Chapter 57). Nevertheless, because the excitability of motor neurons is dependent on descending excitatory and inhibitory signals, absent or hypoactive stretch reflexes can also result from lesions of the central nervous system. Hyperactive stretch reflexes, conversely, always indicate that the lesion is in the central nervous system.

Interruption of Descending Pathways to the Spinal Cord Frequently Produces Spasticity

The force with which a muscle resists being lengthened depends on the muscle's intrinsic elasticity, or stiffness. Because a muscle has elastic elements in series and parallel that resist lengthening, it behaves like a spring (Chapter 31). In addition, connective tissue in and around the muscle may also contribute to its stiffness. These elastic elements may be pathologically altered following brain and spinal cord injury and thereby cause contractures and abnormal joint positions. However, there is also a neural contribution to the resistance of a muscle to stretch; the feedback loop inherent in the stretch reflex pathway acts to resist lengthening of the muscle.

Spasticity is characterized by hyperactive tendon jerks and an increase in resistance to rapid stretching of the muscle. Slow movement of a joint elicits only passive resistance, which is caused by the elastic properties of the joint, tendon, muscle, and connective tissues. As the speed of the stretch is increased, resistance to the stretch rises progressively. This phasic relation is what characterizes spasticity; an active reflex contraction occurs only during a rapid stretch, and when the muscle is held in a lengthened position, the reflex contraction subsides.

Spasticity is seen following lesion of descending motor pathways caused by stroke, injuries of the brain or spinal cord, and degenerative diseases such as multiple sclerosis. It is also seen in individuals with brain damage that occurs before, during, or shortly after birth, resulting in *cerebral palsy*.

Spasticity is not seen immediately following lesions of descending pathways, but develops over days, weeks, and even months. This parallels plastic changes at multiple sites in the stretch reflex circuitry. Sensory group Ia axons release more transmitter substance when active, and the alpha motor neurons change their intrinsic properties and their morphology (dendritic sprouting and denervation hypersensitivity) so that they become more excitable. Changes in excitatory and inhibitory interneurons that project to the motor neurons also take place and probably contribute to the increased excitability.

Whatever the precise mechanisms that produce spasticity, the effect is a strong facilitation of transmission in the monosynaptic reflex pathway. It is not the only reflex pathway affected by lesions of descending motor pathways. Pathways involving group I/II interneurons and sensory fibers from skin are also affected and exhibit the symptomatology observed in patients with central motor lesions. In the clinic, spasticity is therefore used in a broader sense and does not only relate to stretch reflex hyperexcitability. It is still debated whether reflex hyperexcitability contributes to the movement disorder following lesion of descending pathways or whether it may be a pertinent adaptation that helps to activate the muscles when descending input is diminished.

Lesion of the Spinal Cord in Humans Leads to a Period of Spinal Shock Followed by Hyperreflexia

Damage to the spinal cord can cause large changes in the strength of spinal reflexes. Each year, approximately 11,000 Americans sustain spinal cord injuries, and many more suffer from strokes. More than half of these injuries produce permanent disability, including impairment of motor and sensory functions and loss of voluntary bowel and bladder control. Approximately 250,000 people in the United States today have some permanent disability from spinal cord injury.

When the spinal cord is completely transected, there is usually a period immediately after the injury when all spinal reflexes below the level of the

transection are reduced or completely suppressed, a condition known as *spinal shock*. During the course of weeks and months, spinal reflexes gradually return, often greatly exaggerated. For example, a light touch to the skin of the foot may elicit strong flexion withdrawal of the leg.

Highlights

1. Reflexes are coordinated, involuntary motor responses initiated by a stimulus applied to peripheral receptors.
2. Many groups of interneurons in spinal reflex pathways are also involved in producing complex movements such as walking and transmitting voluntary commands from the brain.
3. Some components of reflex responses, particularly those involving the limbs, are mediated by supraspinal centers, such as brain stem nuclei, the cerebellum, and the motor cortex.
4. Reflexes are smoothly integrated into centrally generated motor commands because of the convergence of sensory signals onto spinal and supraspinal interneuronal systems involved in initiating movements. Establishing the details of these integrative events is one of the major challenges of contemporary research on sensory-motor integration in the spinal cord.
5. Because of the role of supraspinal centers in spinal reflex pathways, injury to or disease of the central nervous system often results in significant alterations in the strength of spinal reflexes. The pattern of changes provides an important aid to diagnosis of patients with neurological disorders.

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33

Locomotion

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).

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

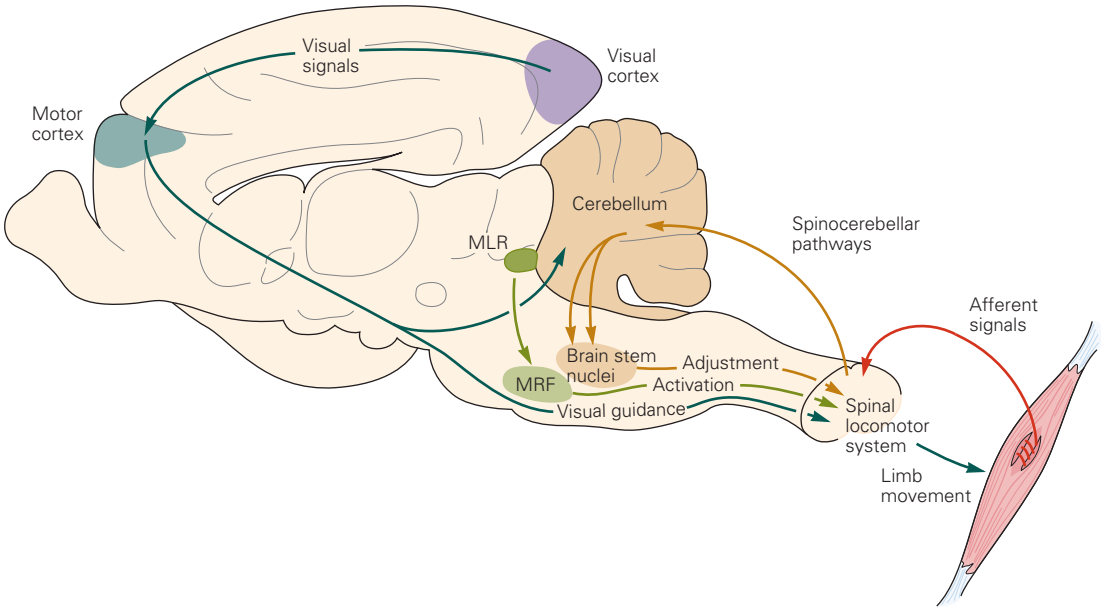


Figure 33–1 The locomotor system. Multiple regions of the central nervous system interact to initiate and regulate locomotion. Locomotor networks in the spinal cord—the central pattern generators (CPGs)—generate the precise timing and patterning of locomotion. Proprioceptive sensory feedback modulates 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.

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.

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

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,

(continued)

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.

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

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).

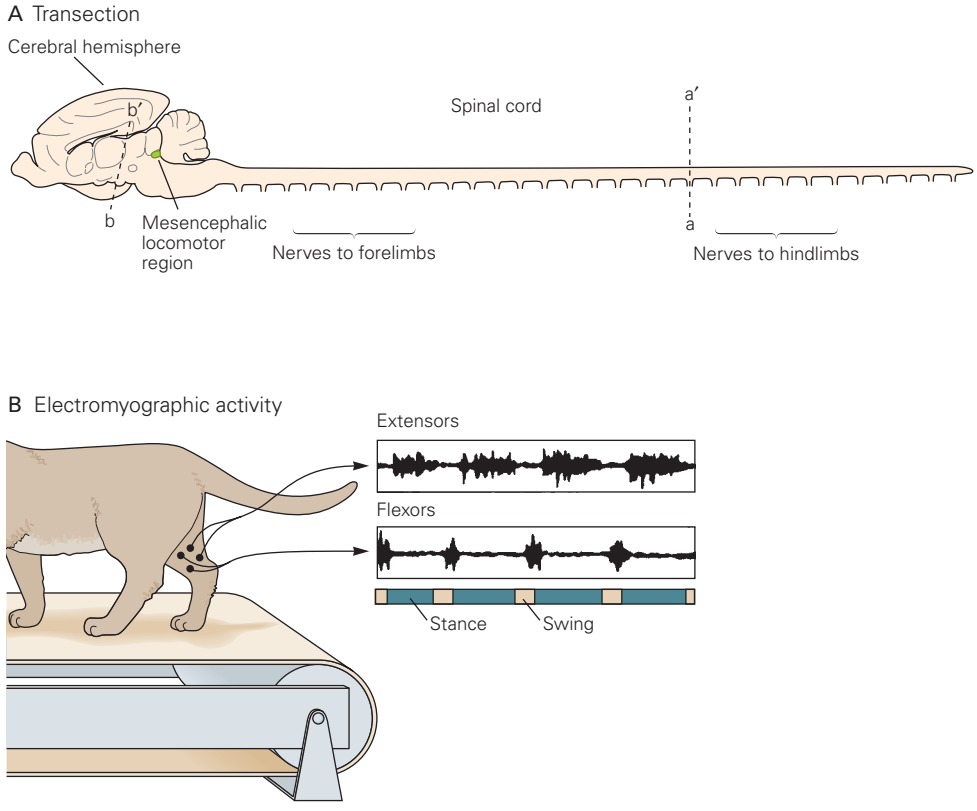


Figure 33–2 Selected animal models used to study locomotor control systems.

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.

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

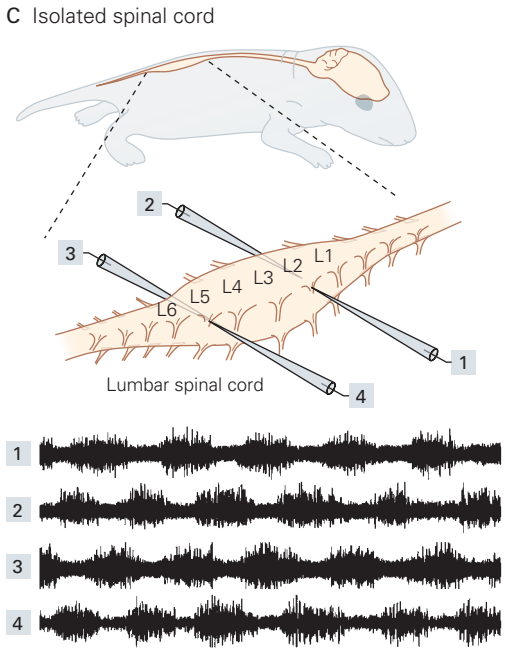
Locomotion requires the production of activity in many muscles that need to be coordinated in a precise rhythm and pattern. The rhythm defines the frequency of the cyclic activity, whereas the pattern defines the spatiotemporal activation of muscle groups within a cycle. In swimming animals, such as the lamprey or the tadpole, locomotion is expressed as a traveling

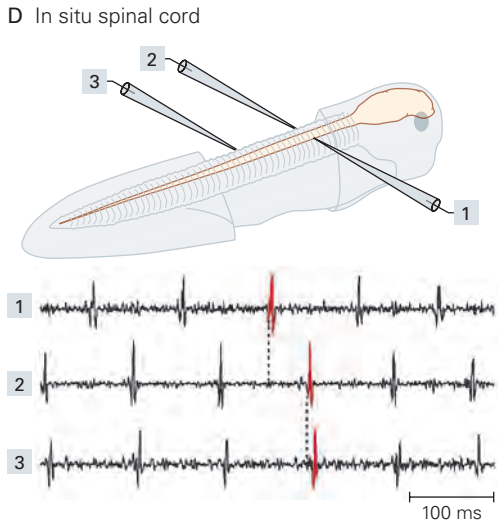
In Vitro Preparations Are Used to Study Central Organization of Networks

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.





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.)

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

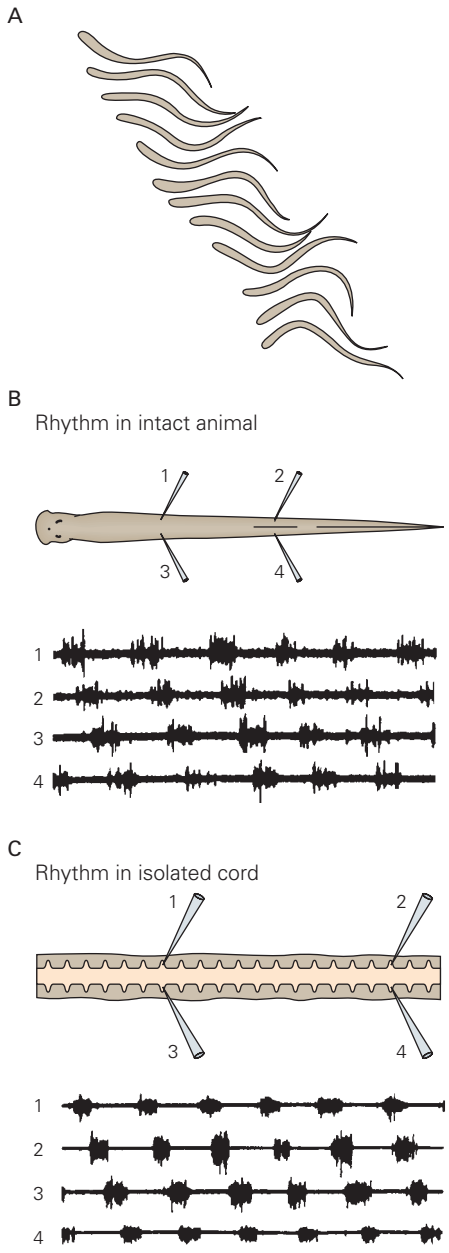


Figure 33–3 Lamprey swimming. The lamprey swims by means of a wave of muscle contractions traveling down one side of the body 180° out of phase with a similar traveling wave on the opposite side (**A**). This pattern is evident in electromyogram recordings from four locations along the animal during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