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Biological Pattern Generation: The Cellular and Computational Logic of Networks in Motion

Review

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In 1900, Ramón y Cajal advanced the *neuron doctrine*, defining the neuron as the fundamental signaling unit of the nervous system. Over a century later, neurobiologists address the *circuit doctrine*: the logic of the core units of neuronal circuitry that control animal behavior. These are circuits that can be called into action for perceptual, conceptual, and motor tasks, and we now need to understand whether there are coherent and overriding principles that govern the design and function of these modules. The discovery of central motor programs has provided crucial insight into the logic of one prototypic set of neural circuits: those that generate motor patterns. In this review, I discuss the mode of operation of these pattern generator networks and consider the neural mechanisms through which they are selected and activated. In addition, I will outline the utility of computational models in analysis of the dynamic actions of these motor networks.

Introduction

In vertebrates, the generation of rhythmic activity in hindlimb muscles, locomotor activity, does not require sensory input but is generated by central pattern generator networks (CPGs). This radical finding emerged from the pioneering studies of Brown (1911) and von Holst (1935) and overturned the then predominant view that complex locomotor behaviors require consecutive reflexes that are chained to one another. To gain general acceptance, however, more detailed studies were needed to firmly establish CPG circuits as a general principle of neural organization in both vertebrates (Grillner and Zangger, 1975; Grillner et al., 1976; Grillner, 1985; Orlovsky et al., 1999; Kiehn, 2006) and invertebrates (see Wilson, 1966; Jing and Weiss, 2005; Kandel, 1979; Kristan et al., 2005; Marder et al., 2005; Selverston, 2005).

We know that in all animals, vertebrates or invertebrates, movements are controlled by CPG networks that determine appropriate sequences of muscle activation (see Grillner, 2003; Selverston, 2005). Each animal is endowed with a broad repertoire of CPGs, located in different regions of the central nervous system (Figure 1) and available for differential activation, thus providing animals with a distinctive set of solutions to accommodate their widely divergent patterns of behavior. For example, the recruitment of different CPGs enables a newborn chicken to perform appropriate hatching movements—to break the eggshell and to stand, walk on two legs, breathe, and to perform the appropriate neck and eye movements to identify and peck grains on the ground, and finally to swallow them.

Although CPGs provide the basis for generation of motor patterns, it is clear that sensory input is, nevertheless, crucial for the refinement of CPG activity in response to external events (Grillner, 1985). If CPGs invariably produced rigidly fixed action patterns, animals would behave like automata—stereotypic robots or soldiers in a parade. In reality, basic CPG activity is subject to adaptation by a variety of sensory mechanisms, such that movements can be adapted dynamically to changes in the environment. CPGs thus provide a flexible and modifiable template—an essential requirement in a demanding and changing world. The adaptations achieved by sensory inputs can be fast—from cycle to cycle, as when running in the forest—or slow, to accommodate the animal's growth. Such adaptations are typically mediated by short- and long-term forms of synaptic plasticity and can be induced by different cellular and synaptic mechanisms through actions at the network level (see below).

Although some CPGs, like those involved in breathing, are active continuously throughout life, most are quiescent under resting conditions and become recruited only when driven by neurons with command functions. A clear-cut example of such top-down control is the command center for locomotion, which is conserved throughout vertebrate phylogeny. This center is located in the midbrain (see Orlovsky et al., 1999) and determines when locomotor CPGs are to be activated and also the level of activity (e.g., fast or slow locomotion).

Defining the underlying logic of CPG programs demands insight and answers to several issues about central motor programs: (1) How distinctive are they? (2) How are they recruited? (3) What are the cellular mechanisms used for pattern generation? I will address each of these three issues in turn and will then provide specific instances of the workings of CPG programs.

The Network Logic of Central Pattern Generators: A Repertoire of CPGs Forms a Species-Specific Motor Infrastructure

In this review, I use the term CPG in a broad sense, denoting any network within the CNS that coordinates a motor behavior or a part thereof. Viewed from this perspective, it is the entire inventory of CPGs that forms the motor infrastructure of a species or an individual (Figure 1) (Grillner, 2003). Let me illustrate this point with a few examples. The simplest case can be represented by the family of withdrawal reflexes that removes the body surface from an irritant. Such reflex responses, finely tuned by sensory experience during the neonatal period, are determined by a set of spinal interneurons (Schouenborg, 2004). More complex CPGs include those that coordinate swallowing, coughing, or sneezing (see Jean, 2001)—they generate a standard pattern that requires timing at the millisecond level, the activation of different muscles in a precise and sequential manner.

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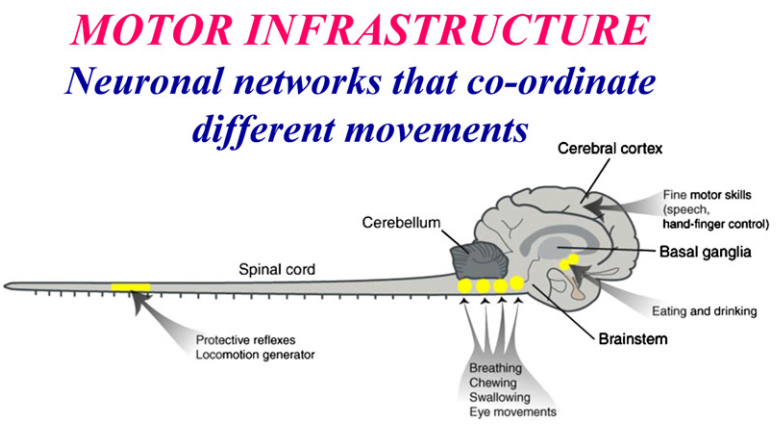

Figure 1. Motor Infrastructure

Along the neuraxis, different motor programs/CPGs are located that can be recruited when needed, from protective reflexes and locomotor CPGs in the spinal cord to respiration and saccadic eye movements at the brainstem level. These different motor programs/networks form together a motor infrastructure. Each motor program can be recruited into action by neural mechanisms that determine when a given motor program should be selected (Grillner, 2003).

CPGs that control rhythmic behaviors like breathing, chewing, and locomotion generate rhythmic neural activity over an extended period (see Feldman and Del Negro, 2006; Grillner, 2003; Combes et al., 2004; Kiehn, 2006; Tunstall et al., 2002). In locomotion, for example, hundreds of muscles are coordinated with precise timing. In all vertebrates, the CPGs for locomotion are located in the spinal cord and are controlled by descending inputs from specific locomotor command regions in the brainstem. A somewhat more complex neural organization is that formed by the motor representation underlying saccadic eye movements. This representation is located in the superior colliculus (tectum) (see Isa, 2002; Sparks, 2002), and a brief intense burst of activity in different locations within the collicular map releases a saccadic eye movement in a given direction and amplitude.

Motor programs also underlie the expression of emotions, as first pointed out by Darwin (1872). Humans express several specific forms of emotions (Ekman, 1973). Some, for example smiling, involve only facial muscles, whereas others, crying and laughing, also recruit the respiratory system. Some of these motor programs, such as that underlying crying, are known to be generated by brain stem circuits, and it is likely that other emotional behaviors are similarly activated—stimulation of the central nucleus of the amygdale, for instance, elicits the expression of fear (LeDoux, 1996). In mammals and birds, warning calls and other innate signals can be elicited by stimulation of the periaqueductal gray region of the midbrain. Finally, different patterns of goal-directed behavior can be triggered by stimulation of hypothalamic structures. These behaviors include attack (sham rage), sexual behavior, and the search for water (Hess, 1949; Andersson, 1978; Pfaff, 1999). In these cases, a sequence of motor programs becomes activated, and the resulting motor acts are adapted well to the surrounding world.

Strikingly, a large part of the standard motor repertoire can be generated spontaneously in animals that lack their cerebral cortex but have the basal ganglia and other parts of the forebrain intact (Bjursten et al., 1976). Decorticate cats walk around, display sham rage, and may even attack other cats. Seemingly, they get hungry, search for food and eat, and can even recall from previous experience the location of the food. These classic experiments tell us that different patterns of behavior can be initiated and coordinated with the help of the remaining forebrain structures, among which the basal ganglia are particularly important for the control and coordination of the different CPGs. But, if the lesions include the basal ganglia, the behavior is fundamentally different, lacking the adaptive component, although individual CPGs can still be activated by appropriate stimuli (Hinsey et al., 1930).

Mechanisms for the Selection of which CPG Should Be Active

How are these central motor programs selected, and once selected, how are they generated? Neuronal mechanisms within the brain select which CPG is to be turned on at any given moment (Figures 1 and 2). In vertebrates, the basal ganglia play an important role in this contextual control (see Grillner et al., 2005a; Hikosaka et al., 2006). Under resting conditions, the output layer of the basal ganglia (the pallidum) maintains different CPG networks and thalamocortical neurons under tonic inhibition. For a behavior to be elicited, the particular CPG (or its input) needs to be disinhibited (Figure 2). To achieve this disinhibition, striatal neurons, the input layer of the basal ganglia, inhibit cells within the pallidum that are responsible for inhibiting particular CPG networks. The striatal neurons can, in turn, be activated from either neocortex (pallium in lower vertebrates) or directly from the thalamus. The responsiveness of striatal neurons to activation can be markedly facilitated by dopaminergic inputs (Figure 2), and deficiencies in dopaminergic innervation result in severe Parkinson-like hypokinetic symptoms in all vertebrates—from lamprey to man (see Grillner et al., 2005c). In contrast, enhanced levels of dopaminergic input result in hyperkinesias—inadvertent initiation of movement. These higher control mechanisms are crucial for the orchestration of CPGs—but they are not the focus of this review. Rather, my aim here is to discuss the organization and intrinsic features of CPG design from a cellular and molecular perspective, taking most of my examples from vertebrate locomotor systems.

The Cellular Logic of CPGs: Basic Mechanisms for Generating Recurrent Burst Activity

In any analysis of the dynamic functioning of neural networks, a close interaction between experimental observation and biophysical modeling is indispensable, since

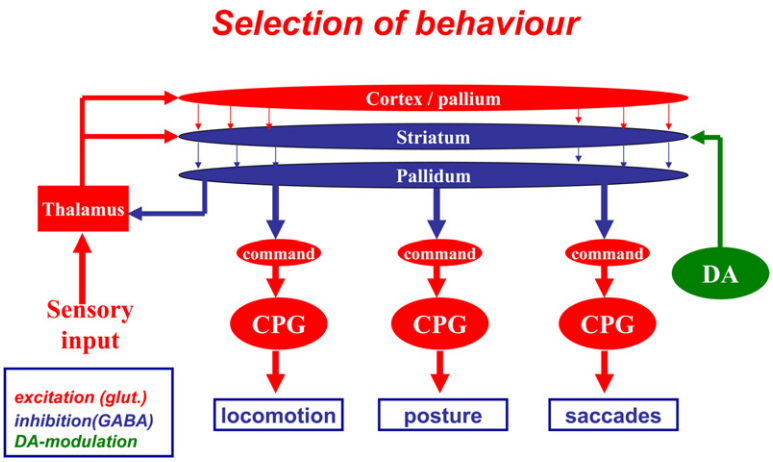

Figure 2. The Basal Ganglia Control CPG Activity—Schematic Diagram

The cerebral cortex in mammals and the corresponding structures in lower vertebrates (pallium) have an excitatory (red) output to striatum, the input layer of the basal ganglia, which is also activated from thalamus directly. Striatum consists of inhibitory (blue) GABAergic neurons (95% projecting medium spiny neurons), which have a very high threshold for activation. They are therefore difficult to activate and may be regarded as a filter for cortical input. Striatum is composed of different subpopulations of neurons. They inhibit the output layer of the basal ganglia, pallidum (several different nuclei), which instead consists of GABAergic neurons with a very high level of resting activity, which keep different CPGs under tonic inhibition. The CPG activity is only released when the appropriate striatal subpopulation is activated and inhibits pallidum, resulting in a disinhibition of the CPGs. The dopamine (DA) input to striatum has a very powerful effect in controlling the responsiveness of striatal neurons. The basal ganglia thus have a very important role in determining which CPGs should be active at a given instant. This diagram only includes what is often referred to as the direct loop, and not the indirect ("braking") loop via the subthalamic nucleus.

interactive processes at the ion channel, synaptic, and network levels are difficult to evaluate intuitively (Grillner et al., 2005a; see Figures 3 and 4). Let us consider a simple case—the generation of a series of recurring bursts required in a locomotor sequence. There are two types of rhythm generating networks: those that use interacting neurons without intrinsic pacemaker properties (Figure 3B) and those that utilize pacemaker neurons or neurons, with plateau properties (Figure 3A). We will initially deal with these networks as separate entities, but in reality most networks examined exhibit a blend of both strategies.

Pacemaker Networks

The simplest case of a burst-generating circuit is a group of pacemaker neurons that are electrically coupled through gap junctions or coupled through chemically mediated synaptic excitation, as with certain neurons within the stomatogastric ganglion of crustaceans (see Selverston, 2005). Pacemaker cells have an inherent ability to oscillate. Different ion channels can generate a pacemaker trajectory (Figure 3A), and the palette of ion channels expressed in a given cell determines the frequency range that the neuron generates—the relative duration of the plateau in the cycle. For voltage-dependent depolarization, three types of channels are commonly used: persistent Na^+ channels, subtypes of Ca^{2+} channels, or NMDA receptor channels (Harris-Warrick, 2002; Wallén and Grillner, 1987; Selverston, 2005; Fransen et al., 2006). For the repolarization that follows the depolarizing plateau phase two types of channels are

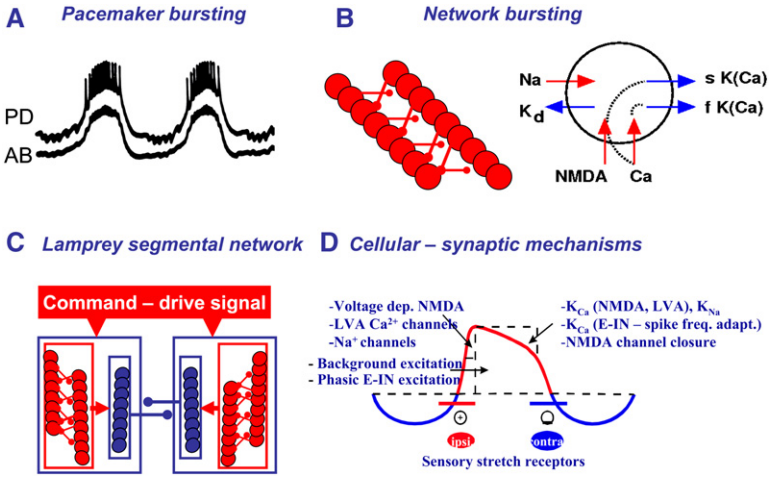

Figure 3. Factors Controlling Burst Onset and Termination

(A) Pacemaker bursting. One way of generating recurring burst activity is by means of pacemaker neurons. The two PD and AB neurons of the stomatogastric system are coupled by gap junctions and are active together (modified from Miller and Selverston, 1982).

(B) Network bursting. A pool of synaptically interacting excitatory neurons can also generate recurring burst activity, if they are coupled together and if they have intrinsic membrane properties that aid in terminating each burst. The diagram to the right summarizes the main cellular mechanisms. Ca^{2+} enters the different cells through both NMDA receptors and voltage-activated Ca^{2+} channels. This leads to a progressive activation of K_{Ca} channels hyperpolarizing the different cells, leading to burst termination.

(C) Reciprocally arranged network similar to that of the lamprey, with excitatory ipsilateral interneurons (red) activating inhibitory neurons (blue) with an action on the contralateral side.

(D) Several different factors that contribute to the initiation of the depolarizing phase, its maintenance, and its termination (lamprey locomotor CPG). In addition to conventional synaptic excitation, voltage-dependent NMDA receptors and low-voltage-activated (LVA) Ca^{2+} channels and Na^+ channels may be activated. Ca^{2+} will enter the cell through these channels, cause activation of K_{Ca}, and thereby a progressive hyperpolarization leading to closure of the NMDA channels. In the behaving animal, the initiation of the depolarizing phase is facilitated by activation of ipsilateral excitatory stretch receptor neurons (SR-E), while the termination of the depolarized phase is partially a result of activation of contralateral inhibitory stretch receptor neurons (SR-I). E, excitatory; I, inhibitory interneuron.

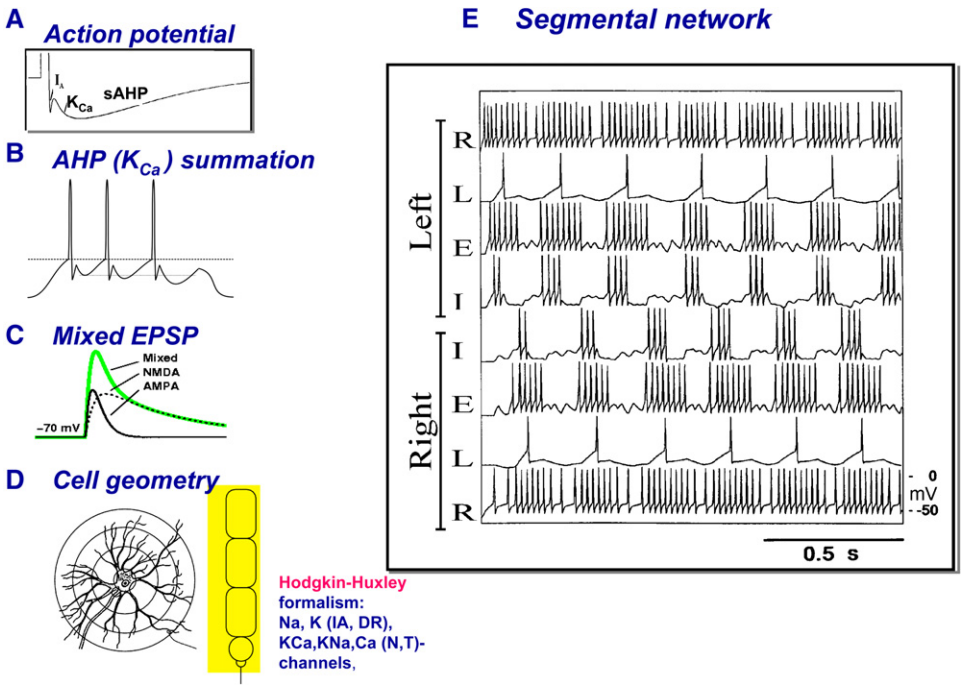

Figure 4. Segmental Model Network for Locomotion as Defined Experimentally

(A) Fast and slow afterhyperpolarization following the simulated action potential.

(B) Summation of K_{Ca}-dependent afterhyperpolarization. Spike frequency adaptation is tuned to correspond to the different neuron types modeled.

(C) Excitatory glutamatergic (NMDA [voltage-dependent] and AMPA) synaptic potentials are illustrated.

(D) The five-compartmental model of a CPG neuron is shown; active properties are located on the soma and initial segment while synaptic inputs are also located further out in the dendritic tree. Ion channels involved in spiking behavior as well as slower Ca^{2+}- or Na^{+}-dependent processes underlying, e.g., adaptation, are modeled based on available data.

(E) Using model neurons corresponding to excitatory and inhibitory CPG neurons that are activated by reticulospinal (R) inputs, the left-right activation pattern as well as an adequate frequency range can be generated in simulations.

commonly used: K_{Ca} channels and the slow I_A channel (see Selverston, 2005; Grillner et al., 2001). The dynamics of Ca^{2+} handling in the neuron is obviously critical for regulating cytosolic Ca^{2+} levels and consequently the degree of activation of Ca^{2+}-dependent processes.

In a neuron, the generation of a burst pattern requires three features. First, voltage-dependent channels need to open at a certain membrane potential to produce the initial depolarization, and they need to remain open to generate a plateau depolarization. Channels with these properties include persistent Na^{+} channels, L-type Ca^{2+} channels, or NMDA receptors. Second, there must be cellular mechanisms—such as an accumulation of Ca^{2+} ions—that can activate K_{Ca} channels that, in turn, will hyperpolarize the neuron (and thereby end the depolarizing phase). This hyperpolarization will lead to a closure of voltage-dependent ion channels and thus a further hyperpolarization, terminating the depolarizing phase of the potential. Third, after burst termination, the opening of K_{Ca} channels will produce a hyperpolarization within neurons of the network, followed by a recovery period in which the cytosolic Ca^{2+} is lowered. In some cells a hyperpolarization-induced slow depolarizing current (I_h) may also be activated. This current, in addition to contributing to excitatory background drive, will trigger a new burst, thereby starting the cycle anew. Ion channels like I_A, the hyperpolarization-activated current I_H, and the low-voltage-activated Ca^{2+} channels (Ca_V 3.1) may contribute to termination of the hyperpolarized phase and boost the depolarization as the membrane potential approaches spike threshold.

"Network Oscillators"

To work together, neurons need to talk to each other. In most cases, burst-generating neurons exhibit some degree of mutual excitation, either by means of synaptic excitation or through gap junctions. To generate each burst, a mechanism is required to activate the neuronal population, maintain activity for a prolonged period, and subsequently to terminate the bursts (Figure 3B).

Burst activity can easily be initiated and maintained, provided that there is background excitatory drive and that there is some type of excitatory interaction within the neuronal network. The mechanism for terminating each burst employs two main strategies. One form, as we have seen, is an activity-induced hyperpolarization produced by the burst-generating neuronal population itself. For example, a progressive elevation in Ca^{2+} level during the burst activity (due to entry through NMDA and Ca^{2+} channels) can activate K_{Ca} channels that will hyperpolarize the neuronal population (El Manira et al., 1994; Grillner, 2003; Hellgren et al., 1992) and arrest neuronal firing (Figure 3B). As soon as a neuron within the bursting network stops spiking, further removal of excitation from other neurons will occur, and this effect will thereby effectively withdraw neurons from the bursting population. Na^{+}- activated K^{+} channels (K_{Na}) are also likely to

contribute to bust termination (P. Wallén, B. Robertson, A. Bhattacharjee, L.K. Kaczmarek, and S. Grillner, 2005, Soc. Neurosci., abstract). Another form of burst termination relies on sets of inhibitory interneurons that feed back onto the excitatory cells and contribute to, or elicit, burst termination.

New bursts, in turn, can be initiated by voltage-activated currents triggered near the threshold for the action potentials, such as those mediated by low-voltage-dependent Ca^{2+} (Ca_V 3.1) or NMDA channels, reinforced by excitation created by synaptic interaction within the neuronal network.

A Few Well-Studied Examples of Simple Circuits that Underlie Behavior

I consider below four examples of the links between simple CPG circuits and behavior that have been studied in some detail: (1) a group of pacemaker neurons from the crustacean stomatogastric system, (2) a vertebrate locomotor burst-generating circuit, (3) a brain stem respiratory circuit, and (4) rhythm-generating circuits in the mammalian hippocampus.

Pacemaker Type

In crustaceans, a small set of neurons in the stomatogastric ganglion coordinates chewing and propulsion of the food. This network contains fewer then 30 neurons and is among the best-studied CPGs (Marder et al., 2005; Nusbaum and Beenhakker, 2002; Selverston, 2005). Neurons of the pacemaker type, such as the PD and AB cells of the pyloric part of the ganglion, are critical for the burst generation (Figure 3A). Other neurons, often referred to as conditional bursters, are activated by external drive signals and can elicit changes in the frequency or other characteristics of the bursting pacemaker cells. Burst-generating neurons of the pacemaker type operate at a certain frequency at rest but adapt over a wide range to external synaptic input that can shorten or prolong the depolarizing phase and overall burst frequency. Hybrid circuits in which some but not all neurons have plateau properties, are typical. Another well-studied dynamic hybrid CPG system with a limited number of cells is that coordinating the heart and circulation in the leech (Hill et al., 2003a).

Locomotor Burst Activity

During walking and swimming, alternating activity between the left and right side of the body is an integral part of the motor pattern. Yet each side can generate burst activity independent of the other side. The segmental unit CPG of the lamprey, for example, depends on a pool of interactive excitatory interneurons (Figure 3B). When the interneuron pool is activated by a tonic excitatory drive, it responds with burst firing. Neurons within the interneuron pool may fire only one or a few spikes per burst, and in this case inhibition is not required for burst termination. Rather, termination is achieved through the progressive activation of K_{Ca} channels during the bursts (due to the Ca^{2+} entry; Figure 3B), resulting in hyperpolarization of interneurons (see Cangiano and Grillner, 2005; Grillner, 2003; Hellgren et al., 1992). In addition to this fast mode of termination, the lamprey locomotor network operates in a slow mode that depends on NMDA receptor-mediated plateau-potentials in a population of excitatory interneurons. In this instance, burst termination also results from Ca^{2+} accumulation and activation of K_{Ca} (Figures 3B and 3D) and possibly K_{Na} channels (Cangiano and Grillner, 2003, 2005; Wadden et al., 1997; Wallén and Grillner, 1987).

Respiratory Core Activity

Breathing is controlled by a brainstem network that is continuously active from birth to our last breath. This network has several components, one of which is the nucleus of the Prebotzinger complex, often considered to be the excitatory kernel that drives follower nuclei (Smith et al., 1995; Gray et al. 2001). This network can generate respiratory bursts in slices without inhibitory mechanisms, an activity that depends solely on excitatory interactions. In the presence of AMPA receptor antagonists, a proportion of these neurons continue to burst at approximately the same rate, but they are now independent (Smith et al., 1995). Thus some neurons in the Prebotzinger complex are pacemaker neurons in which persistent Na^+ channels drive the oscillations at the single-cell level. This distributed property has the advantage of providing a more stable rhythm at the network level and over a large range of frequencies (Butera et al., 1999). Only a proportion of participating pacemaker neurons need to be inherent bursters. The critical role of the pacemaker neurons in the rhythm generation within the prebotzinger complex has, however, recently been questioned. It appears that a complementary system of synaptic interaction can generate respiratory burst activity independently of pacemaker properties (Feldman and Del Negro, 2006). If this proves correct, there may be complementary sets of mechanisms, designed to ensure that the respiratory system continues to operate under all conditions (Figures 3A and 3B).

Hippocampal Gamma Rhythm

An example of a network based on an inhibitory neuron terminating each burst is that generating the fast hippocampal gamma rhythm (20–80 Hz). It is generated by pyramidal cells that excite each other (mutual excitation) and also by fast inhibitory interneurons (e.g., basket cells) that spike with brief action potentials and have a brief afterhyperpolarization. The inhibitory interneurons thus become activated by the pyramidal neurons with a synchronous barrage of EPSP, and they in turn produce strong feedback inhibition to the soma of pyramidal neurons. Once silenced, the pyramidal cells will fire again as on postinhibitory rebound and thereby generate a new cycle (see Grillner et al., 2005b; Hajos et al., 2004). The postinhibitory rebound excitation can be generated by a hyperpolarization-activated inward current like a low-threshold Ca^{2+}current. The brief afterhyperpolarizations of the inhibitory basket cells allow for a high burst rate in the gamma range.

Hippocampal Theta Rhythm

The theta rhythm of the hippocampus is substantially slower (4–12 Hz) than the gamma rhythm. It is dependent on the interaction between pyramidal neurons and a different type of inhibitory interneuron (O-LM cells) with a longlasting afterhyperpolarization, and it projects to the distal dendrites of the pyramidal cells that mutually excite each other. The distal dendrites have very different membrane properties. They have a long afterhyperpolarization following the action potentials, dependent on a K_{Ca} current, but they also express an I_h current, a hyperpolarization-activated inward current that will turn on rather slowly, depolarizing the cells.

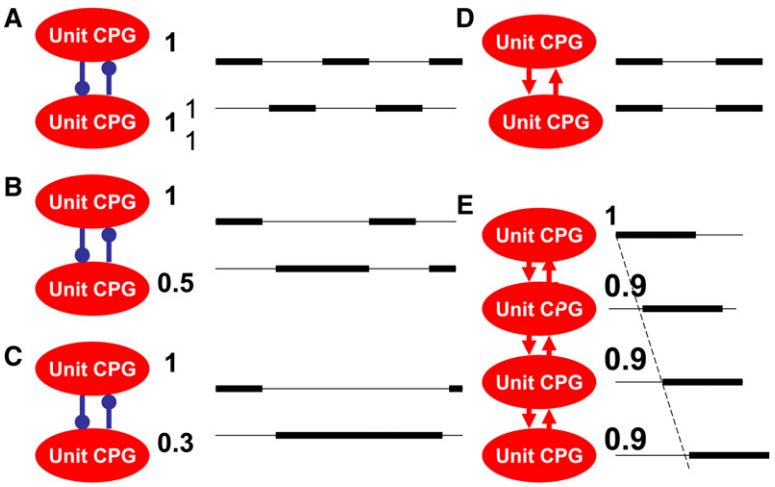

Figure. 5. CPG Configurations Producing Different Types of Motor Coordination

(A) Two unit CPGs (each producing recurring bursts) with the same excitability (indicated as 1 arbitrary unit) generate symmetric alternation if they are connected by reciprocal inhibition (blue).

(B and C) When the excitability of one unit CPG is reduced (0.5 or 0.3), it will slow down. The net result is an asymmetric activity with one unit CPG generating longer burst and the other the same duration burst as before (excitability 1). This pattern of coordination with one fixed phase (swing) and one that can be varied extensively (support) occurs during walking.

(D) Mutual excitation between the two unit CPGs results in simultaneous bursts, as in a gallop.

(E) Chain of unit CPGs with mutual excitation between each neighbor. If the uppermost unit CPG has a higher excitability (1) than the other unit CPGs (0.9), it will take the lead, and the others will follow with a phase lag, similar to what occurs during undulatory locomotion like that of the lamprey.

These properties of the O-LM cells contribute to the much slower rhythm—they are designed not to fire more than once per theta cycle (see Grillner et al., 2005b; Hajos et al., 2004).

Complex Patterns of Activity—Coordinating Unit CPGs

Alternating Patterns of Activity

Vertebrate networks that control swimming in the lamprey, fish, tadpole, and newt (see Buchanan, 1999; Bem et al., 2003; Tunstall et al., 2002; Grillner, 2003; Masino and Fetcho, 2005) are arranged, at the segmental level, with reciprocal inhibition between the left and right sides of the body. The core of the spinal network in the lamprey consists of excitatory interneurons (EIN) that excite each other within the pool and at the same time activate commissural inhibitory interneurons that inhibit the contralateral CPG (Figure 3C) (Cangiano and Grillner, 2005; Hellgren et al., 1992; Tegnér et al., 1997). This network is activated from the brainstem, by command—drive signals. Several cellular and synaptic mechanisms operate throughout such a cycle (Figure 3D). The initial depolarization is due to (1) the excitatory drive from the brainstem, (2) excitation from other EINs, and (3) a boost in depolarization caused by voltage-dependent channels, notably NMDA- and LVA-activated Ca^{2+} channels. In turn, Ca^{2+} entry during the depolarization leads to a progressive activation of K_{Ca} channels during the depolarization, which in turn results in a hyperpolarization, a closure of NMDA channels, and termination of the burst.

Modeling of network activity provides a test of whether the biological information gathered on the molecular, cellular, and synaptic properties is sufficient to account for the behavior. This would be impossible to arrive at by intuition since there are many dynamically interactive processes. In the interplay between experiments and modeling, a number of questions arise that need to be tested experimentally. It should also be noted that the power of modeling is in disproving faulty hypotheses—and exploring potential solutions.

To analyze further the factors that contribute to the operation of the network, the segmental network from the lamprey has been simulated, based on detailed modeling of neuronal properties that include the summation of the afterhyperpolarization during burst activity (Figures 4A and 4B) and synaptic transmission via AMPA- and voltage-dependent NMDA receptors (Figure 4C). The simulated network with populations of cells of each subtype has been connected according to constraints established in biological experiments. When drive signals from the brainstem reticulospinal system (R) are activated, the network is activated, which in turn generates rhythmic burst activity in the extensive range displayed by the biological network (0.2–10 Hz). A unit CPG can be defined as each group of neurons that can generate a recurrent burst, even if it is normally part of a larger CPG network with many modules. Two such unit CPGs that are reciprocally coupled and therefore generate alternating activity as occurs in the segment of a lamprey or a tadpole are shown in Figure 5A.

Walking—A Form of Asymmetric Alternating Activity

Consider the more complicated general case of walking as a behavioral output of CPG network activity. Here the swing phase of the locomotor step cycle of one limb remains largely constant, whereas the support phase can vary 10-fold or more, from slow to fast locomotion (see Grillner, 1981). When the original burst rate is similar in two reciprocally coupled unit CPGs (of identical design), they will generate symmetric alternation (Figure 5A). If, however, the excitability is lower in one unit CPG than in the other, the result will be asymmetric activity (Figures 5B and 5C) such that the slow unit CPG will determine the duration of the longer burst. In turn, this change will generate a prolonged inhibition of the fast side, thereby delaying the occurrence of a new burst of the fast unit CPG. In addition, the fast unit CPG will determine its own burst duration, due to an inherent burst-terminating mechanisms (cf. Wadden et al., 1997). The

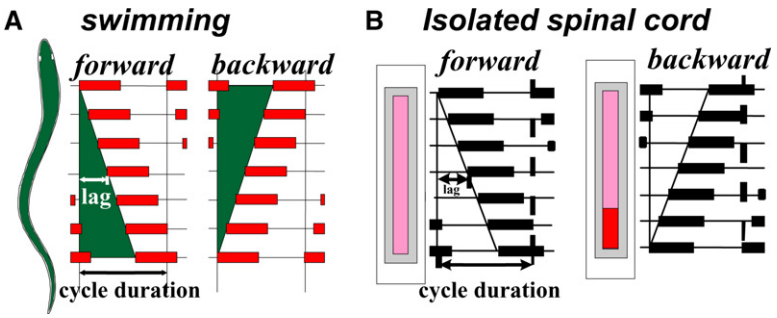

Figure 6. Intersegmental Coordination through Phase Coupling—Undulatory Locomotion

(A) Cyclostomes, fish, and some amphibians and reptiles swim by producing a mechanical wave that is transmitted along the body. As illustrated during forward locomotion, there is a lag between consecutive segments in the spinal cord. This lag is always a certain proportion of the cycle duration and is therefore referred to as a constant phase lag. During backward locomotion the wave is instead propagated from tail to head.

(B) In the isolated spinal cord (control) a rostrocaudal phase lag can also be produced, and thus the ability to generate a constant phase lag is inherent to the spinal cord. The pattern can be reversed if extra excitation is added to the caudal spinal cord (right). This is explained by the fact that the segments of the caudal part then get a higher excitability and would generate a somewhat higher burst rate that is able to entrain the segmental networks in the rostral part of the spinal cord. The rostral segments then have a lower inherent burst rate and will therefore be entrained, but with a certain lag.

asymmetric activity characteristic of terrestrial locomotion can therefore be generated by the interaction of individual unit CPGs, and one would have to assume that the command to the unit CPGs controlling swing and stance would be separate.

Gallop—An Instance of Mutual Excitation between CPGs

If two unit CPGs provide mutual excitation (Figure 5D) as during gallop, they become synchronized, provided they share the same inherent frequency. One instance of such behavior is found in the coordination between the hindlimbs during a gallop or a bound (Orlovsky et al., 1999). If, however, the inherent frequency of the two unit CPGs differs, the situation becomes more complex. In the simple case with unidirectional excitation, one CPG provides the excitation that if faster than the follower unit CPG will determine the burst rate. If the excitability difference is not too great, however, the unit CPG that provides the excitation will pull the other along by providing additional excitation. As in some gaits, however, the follower unit CPG will start its burst with a delay.

Undulatory Locomotion—A Chain of Oscillator Networks

The spinal circuits that generate the undulatory wave that underlies swimming in fish, lamprey, and amphibians can, in a simplified way, be regarded as a series of oscillator circuits (see Grillner, 1974, 2003; Bem et al., 2003; Chevalier et al., 2006; Figure 6A). Normally, rostral segments are activated first, and the other segments follow from head to tailfin with a fixed phase lag of ~1% of the cycle duration (lamprey). This phase lag is evident whether the swimming frequency is low or high. The constancy of the lag phase results in an electromyographical and mechanical phase lag from head to tail of about one cycle, or 100%—a sinusoid with increasing amplitude toward the tail. If the opposite situation is induced with a higher relative excitability in the caudal segments—by inhibition of the rostral segments or additional excitation of the most caudal segments—the direction of the wave will be reversed, and will instead flow from tail to head and backward swimming will result, a behavior of relevance for cornered lampreys (Islam et al., 2006).

Similarly, forward and backward coordination with a constant phase coupling can be generated experimentally in the isolated spinal cord (Figure 6B). The ability to generate burst activity is distributed along the spinal cord, and if isolated, each segment, or even hemisegment, can generate rhythmic burst activity (Wallén and Williams, 1984; Cangiano and Grillner, 2005). Normally a rostrocaudal wave is generated, but if the caudal segments have a higher excitability than the rostral segments, they will take on the lead (Matsushima and Grillner, 1992) and a caudorostral wave is generated. In the lamprey, the axons of EINs are asymmetric with a descending branch extending over five to six segments and a rostral branch extending about three segments. In this way a continuous rostrocaudal network along the spinal cord is formed.

How is this type of flexible phase coupling along the spinal cord achieved? One may consider such coupling in a simplified way, as a series of unit CPGs coupled in a chain with excitatory connections between the different unit CPGs in both directions (Figure 5E). In this case, the unit CPG with the highest inherent frequency will set the phase (uppermost in Figure 5E), and the other unit CPGs will follow—the trailing unit will be the one with the lowest inherent excitability.

The neural mechanisms that operate to generate such a distributed flexible phase coupling for both rostral and caudal swimming have been analyzed extensively through modeling (Wadden et al., 1997; Kotaleski et al., 1999). A hemisegmental "biophysically realistic" model network, as described above (Figure 4), has been extended in the rostral and caudal direction with up to 100 segments and the EINs arranged with appropriate rostrocaudal connectivity. Such a network can be made to display a constant phase lag along the spinal cord—similar to that found in the isolated hemicord (cf. Figure 5E). If, instead, the entire spinal cord is modeled with two such extended EIN networks in parallel and, in addition, a reciprocal inhibitory coupling on the segmental level, the two sides will alternate at each segment. But in addition there will be a phase lag along the simulated spinal cord (Figures 7A and 7B). A simplified version of such a network has been used to control a neuromechanical model of the lamprey (Figure 7C), generating swimming movements in the simulated water (Ekeberg and Grillner, 1999) and also realistic turning behaviors such as pitch, yaw, and roll (see Grillner, 2003).

The Modular Design of CPGs

Mammals can walk, trot, and gallop and sometimes employ a variety of other gaits, revealing several different

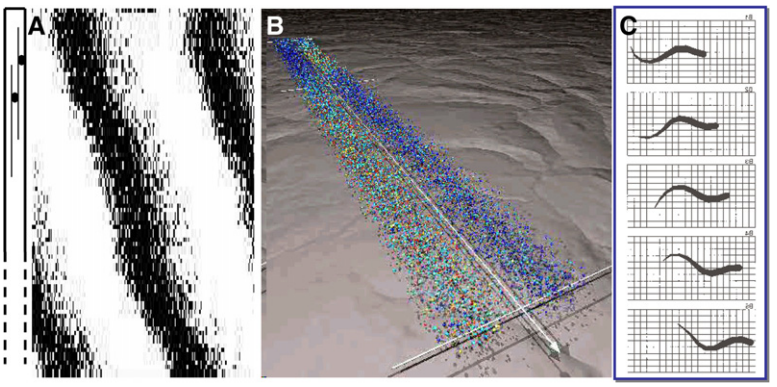

Figure 7. Simulation of Undulatory Locomotion

(A) Simulation of the intersegmental coordination during forward swimming. The action potentials of different excitatory interneurons along the spinal cord are represented with one dot from rostral to caudal (ordinate) and time along the abscissa. The lag along the cord is constant between different segments. The rostrocaudal extent of the axons of the EINs is schematically represented to the left. (B) A full-scale simulation of 60 segments is illustrated in which the activity along the cord is shown. Each dot is one neuron (Hodgkin-Huxley type). Blue dots represent neurons with active inhibition, red dots spiking neurons, and yellow dots depolarized but not spiking neurons (Kozlov, Lansner and Grillner).

(C) Neuromechanical simulation of lamprey swimming.

strategies of coordination. Each limb is controlled by a separate spinal CPG network that provides a standard pattern of activation of the muscles of that limb. Each limb CPG is thus part of a system of interacting limb CPGs (Grillner, 1981) that can be coupled in a few stable modes, alternation or in-phase coordination, as in a walk or a gallop, respectively (Figure 8, left). Each limb CPG can also be used in isolation or in combination, as in a circus dog walking on its hindlimbs or a human walking or running.

We can also walk forward, backward, sideways, and on our knees, which requires a considerable flexibility in the underlying neural circuitry in each limb CPG. For many patterns of motor behavior, CPGs can be further subdivided into smaller functional modules, which can be recombined to generate a varied and flexible motor output. Limb CPGs (Grillner, 1981, 2003) are thought to be composed of a series of "unit CPGs," each controlling a group of close synergists like hip flexors or ankle extensors (Figure 8, middle). The advantage of such a system over a hardwired inflexible network for the entire limb is that it adds considerable flexibility. Changing the mode of interaction (Figures 5A and 5D) between the different "unit CPGs," in much the same way as between the limb CPGs, can lead to changes in motor pattern. With a hardwired system that encompasses the entire limb, a separate network is needed for each type of locomotion. The turtle scratch reflex is similarly organized with modular units that can be recombined (Stein and Daniels-McQueen, 2002). The recombination of discrete unit CPGs in different ways raises the possibility that they can also be integrated into other patterns of motor behavior (Grillner, 1985).

A type of unit CPG can also be allocated to spinal modules controlling groups of synergist muscles that are relevant to posture and static limb position (see

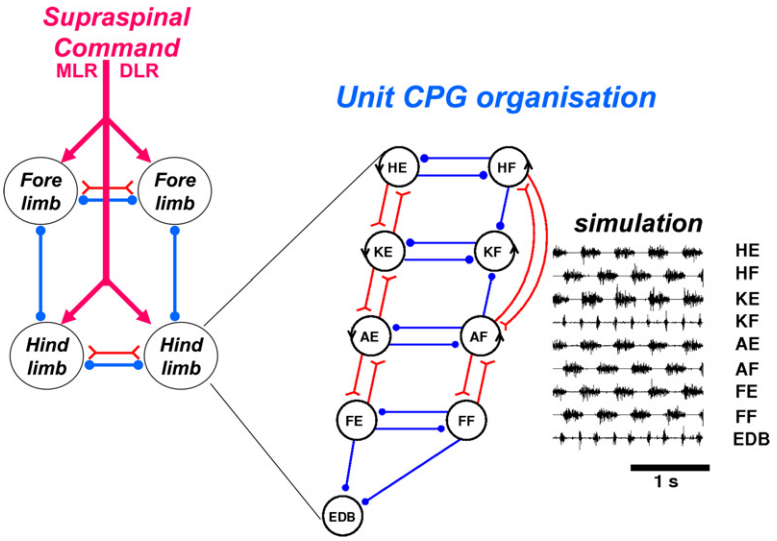

Figure 8. Systems of Interacting CPGs—Inter- and Intralimb Coordination

(Left) The command regions in the brainstem (the mesencephalic [MLR] and the diencephalic locomotor [DLR] regions) control the level of activity in the CPG networks for each of the four limbs. Each limb CPG is responsible for the complex motor pattern of that limb, whereas the interlimb coordination as in walking or a gallop results from the interaction between the different limb CPGs. The interaction takes place through inhibitory reciprocal interaction (blue inhibitory) during walking and excitatory mutual excitation during a gallop (red). (Middle) Within each limb CPG there is most likely a further subdivision in unit CPGs controlling the synergists at one joint like hip (H), knee (K), ankle (A), and foot (F) extensors (E) or ankle (A) flexors (F). Extensor digitorum brevis (EDB) has a particular pattern. The normal pattern of activity results from the interaction between the different unit CPGs at different joints. The advantage is that the unit CPGs could be recombined as in backward or forward walking, in the same way as with the different limb CPGs that can be recombined in the different gaits. Circles indicate inhibition, and forks/triangles excitation. (Right) Exploratory simulation of locomotor activity, with a network arranged as in the diagram in which each unit CPG is designed in a similar way to the lamprey unit CPGs consisting of 100 excitatory interacting neurons—and the interaction between the nine unit CPGs arranged as in the middle diagram. The output of the activity captures essential features of the locomotor output.

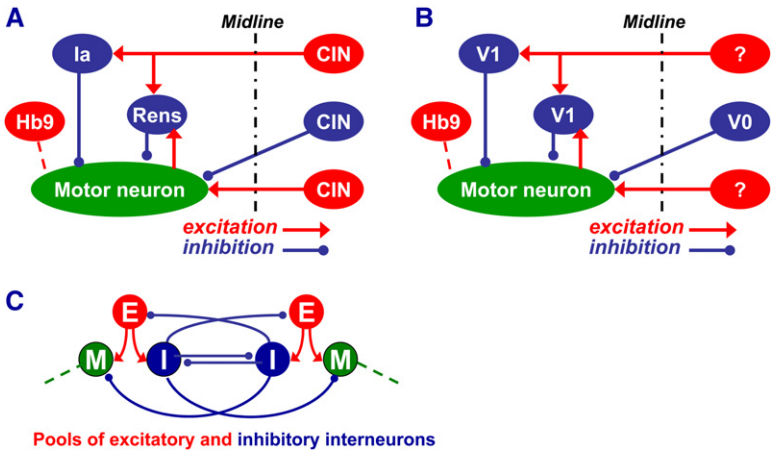

Figure 9. Neuronal Elements in the Hindlimb Walking CPG and the Lamprey CPG

(A) Ipsilateral inhibitory premotor interneurons (1a and Renshaw [Rens]) are known to be rhythmically active during locomotion. They receive input also from contralaterally projecting interneurons. Motoneurons receive input directly from both excitatory and inhibitory contralateral interneurons. One ipsilateral glutamatergic locomotor-related interneuron (Hb9) has also been identified (see Kiehn, 2006).

(B) The same diagram as in (A) except that the identity of the cells within the V0 to V3 classification is indicated.

(C) For comparison, the neuronal core elements of the lamprey segmental CPG are represented that can account for the rhythmic alternating burst activity. E, excitatory interneuron (red); I, inhibitory commissural interneuron (blue); and M motoneuron.

dAvella and Bizzi, 2005; Poggio and Bizzi, 2004). Coactivation of different modules produces different limb positions. Similar modules can also account for the family of different site-specific protective reflexes in the limb (Schouenborg, 2004). This strategy of modular organization applies to a variety of systems both in vertebrates and invertebrates (see Buschges, 2005; Grillner, 2003; Schouenborg, 2004). It would seem likely that these different spinal modules—integrated circuits—can also be recruited during "voluntary" limb movements (Grillner, 1985; Schouenborg, 2004) like wriggling the big toe or for adaption of the human locomotor synergies to other gross movements like skiing or bicycling.

Unit CPGs may therefore exist for each group of close synergists at a given joint (Figure 8). This view posits that although each unit CPG can burst by itself, its final pattern depends on three factors: (1) the reciprocal interaction between antagonists (flexors and extensors) at the same joint, (2) mutual excitation between unit CPGs at different coactive joints, and finally (3) the possibility of more complex patterns with individual muscles being active in the interval between the main flexor and extensor bursts. This conceptual scheme has been tested in an exploratory fashion using the segmental unit CPGs defined in the lamprey (Figure 4), introducing them as unit CPGs in the limb system. With no further modification, the motor pattern of the hindlimb and also the complex pattern of activity of the different muscles of the limb could be simulated (Figure 8, right). Although the limb CPG is likely to be more complex, the idea that a distributed circuit of this type can reproduce the motor pattern and add the flexibility of reconfiguring the network to other patterns of coordination is a provocative one.

A Search for the Neural Underpinning of Mammalian Locomotor CPGs

The elucidation of the mammalian locomotor CPG has been more demanding than that of the tadpole or the lamprey. In the latter cases, segmental motor pattern can be achieved by the symmetric alternation between left and right by pools of excitatory and crossed inhibitory interneurons (Figure 9C). In contrast, mammalian locomotion depends on a more complex pattern of muscle activity in each limb, a pattern that is coordinated by the limb CPG. The locomotor pattern in the lumbosacral spinal cord has received most attention. Here locomotor patterns can be induced in the isolated rodent spinal cord, even when the dorsal aspect has been removed, revealing that circuits sufficient to control locomotion reside in the ventral spinal cord. Moreover, in each hemicord the motor pattern of a limb can be produced after isolation of each side (see Kiehn, 2006). In rodents, CPG circuitry of each limb appears to be distributed along the spinal cord, as in the lamprey, although the more rostral segments that control the proximal hip joint appear to have a more powerful role in entraining circuits that control the knee, ankle, and foot joints (see Grillner, 1981; Rossignol et al., 2006; Kiehn, 2006). Inhibitory mechanisms are, of course, required to elicit alternating flexor and extensor activity. After inhibition has been blocked pharmacologically, burst activity commences, indicating that here also the core excitatory burst-generating circuit does not require inhibition to generate burst activity.

Detailed information from the cat spinal cord continues to contribute importantly to studies of locomotion (Jankowska, 2001; McCrea, 2001). But remarkable recent progress has come recently from the development of an in vitro preparation of the neonatal rodent brainstem and spinal cord (Kudo and Yamada, 1987; Butt et al., 2005; Kiehn and Butt, 2003; Kiehn and Kullander, 2004; Wilson et al., 2005). Although details of the CPG network are still not clear, commissural excitatory and inhibitory premotor interneurons have been identified, as have ipsilateral excitatory interneurons (Figure 9A; Butt et al., 2005; Kiehn and Kullander, 2004; Lanuza et al., 2004; Wilson et al., 2005). Novel developmental findings in the mouse have led to the genetic delineation of subtypes of precursor interneurons (V0–V3) that give rise to some of the classical types of spinal interneurons (Jessell, 2000). V0 and V3 give rise to neurons that project to the contralateral side, while V1 and V2 neurons are largely ipsilateral (Figure 9B). Among the V1 interneurons are the inhibitory 1a and Renshaw premotor interneurons that are active during locomotor activity (Figures 9A and 9B). The V2 group contains both inhibitory and excitatory interneurons.

These genetic markers have opened up the possibility of expressing genetically encoded fluorescent probes (e.g., green fluorescent proteins) or other molecules such as receptors in specific subtypes of interneurons (Gosgnach et al., 2006; Kiehn and Butt, 2003; Kiehn and Kullander, 2004; Lanuza et al., 2004; Wilson et al., 2005). These methods have markedly facilitated the demanding nature of intracellular recordings from pairs of identified neurons. The synaptic connectivity and characteristics, as well as the biophysical properties of the different cell populations, however, still need to be understood. Genetics has shown that the V0 interneurons contribute to the left-right alternation through crossed inhibitory effects or motor neurons (Lanuza et al., 2004; Figure 9). And in an elegant technical development (Lechner et al., 2002; Gosgnach et al., 2006), interneurons of one subtype (V1) have been engineered to express an invertebrate G protein-coupled receptor molecule to an inward rectifier ion channel. When these receptors are activated pharmacologically, they hyperpolarize V1 neurons without interfering with the activity of other neurons. During network activity one can thus remove a given subtype of cell from the circuit and observe whether it affects the burst activity—in this case it appears that CPG activity slowed (Gosgnach et al., 2006).

There is, however, yet a finer level of motor circuit organization in the spinal cord. Each major group of interneurons, for instance V1 neurons (Figures 9A and 9B), is in reality composed of a number of discrete subpopulations, each concerned with the control of individual motor nuclei. The organization of these premotor interneurons and how they interact during movement needs to be understood better. A combination of developmental, molecular, and neurophysiological techniques promises to yield rapid progress in the understanding of the neuronal basis of motor coordination in mammals.

Network Properties Can Be Radically Modified via G Protein-Coupled Receptors

We have discussed the network operation in terms of the fast synaptic interaction on the millisecond level acting via ionotropic glutamate, glycine, and GABA receptors ($GABA_A$). At all levels of CNS there are also slower forms of synaptic transmission mediated by metabotropic receptors acting at second, minute, or hour timescales. These transmitter systems influence not only mood and attention, but they also fine-tune a variety of sensory and motor functions. These systems include peptidergic, aminergic (5-HT, noradrenaline, dopamine), endocannabinoid, nitric oxide, and metabotropic glutamate ($mGluR_{1-7}$) and GABA receptors ($GABA_B$). Each of these receptors may change the properties of a network by modifying the action of specific cellular and synaptic targets—for instance by phosphorylating a specific ion channel subtype. Practically all networks analyzed, whether vertebrate or invertebrate, are subject to many forms of modulation that can fundamentally modify cellular and network properties. The functional significance of this type of modulation is presumably to be able to adapt and optimize the function of a network to varying behavioral demands. A wealth of information has emerged from different vertebrate and invertebrate model systems, but for reasons of space I will illustrate general principles using three examples from the lamprey system (see Table 1).

The lamprey CPG is embedded in a number of modulatory systems (see El Manira and Wallén, 2000; Grillner, 2003), some of which are activated as soon as the network starts to operate. Neurons of the spinal 5-HT system are located in the midline where they form a dense plexus, from which 5-HT is released in a paracrine fashion onto the dendrites of network interneurons (see Christenson et al., 1991). 5-HT reduces the current carried through N-type Ca^{2+} channels (Hill et al., 2003b), which in turn results in a reduction of the amplitude of the slow K_{ca}-dependent afterhyperpolarization (sAHP) (Wallén et al., 1989; Biro et al., 2006). In addition, 5-HT has presynaptic inhibitory effects on excitatory synapses (Hill et al., 2003b). The 5-HT-mediated reduction of the K_{Ca} current results not only in a reduction of the sAHPs but also in a higher frequency of action potentials and a reduced spike frequency adaptation. The net effect at the network level is a reduced burst frequency—with longer and more intense bursts and a more regular burst pattern. The 5-HT system thus contributes to the operation of the CPG by modifying the properties of the network interneurons—and the transmitter they release at their synapses. 5-HT appears to be involved in the control of most vertebrate locomotor networks. Indeed, in mammals as in the lamprey, the raphe-spinal and parapyramidal 5-HT neurons are turned on as locomotion begins (Jacobs and Fornal, 1997; Liu and Jordan, 2005).

Metabotropic glutamate receptors (El Manira et al., 2002) are activated as soon as glutamatergic neurons become active during locomotion. One subtype, $mGluR_1$ (Kettunen et al., 2005), is activated during locomotor activity and acts to speed up locomotor activity through several distinct cellular mechanisms, mediated in part by phospholipase C-protein kinase C and IP_3 pathways. $MGluR_1$ activation enhances the NMDA receptor current, reduces a leak conductance, and triggers the release of endocannabinoids, which in turn reduces glycinergic synaptic current from contralateral neurons, via a presynaptic action. These three cellular mechanisms are convergent and produce a net excitatory and stabilizing effect on the network.

Tachykinins (including substance P) are released during activity in the locomotor network and exert an excitatory effect to induce a more regular burst pattern (Parker et al., 1998; C. Perez Thorn, R.H. Hill, and S. Grillner, 2005, Soc. Neurosci., abstract). When the action of tachykinins is blocked by receptor-specific antagonists, burst frequency is reduced. Similarly to $mGluR_1$, the tachykinins act via a protein kinase C-mediated facilitation of NMDA currents. The tachykinins also modify the activity-dependent synaptic plasticity in crossed inhibitory synapses—although the first IPSP in a spike train may be unchanged, the subsequent IPSPs decline in amplitude much faster than under control conditions enhancing burst frequency (Parker and Grillner, 1999). If tachykinins are applied in high concentrations, their action may last over 24 hr.

Although fast synaptic actions determine motor pattern in a given instant, the response pattern of the neurons and the efficacy of their synapses are, to a large

Table 1. Metabotropic Amino Acid, Aminergic, and Peptidergic G Protein-Mediated Modulation of Ion Channel, Synaptic, Cellular, and Network Activity in the Lamprey Spinal Cord

	Presyn. gating	Ca_v3 (LVA)	$Ca_v2.1$-2.2 (HVA N P/Q)	IP3	SK1-K_{Ca}	K_{Na}	K^+	NMDA	Network (frequency)
$GABA_B$	*Inh*	↘	↘		(↘)	*0*			↘
$mGluR_1$	*0*	*0*	*0*			*0*	↘	↗	↗
$mGluR_5$	*0*	*0*	*0*	Ca^{2+} osc ↗		*0*			↘
$mGluR_{II-III}$	*Inh*		*0*			*0*			↘
$5\text{-}HT_{1A}$	*Inh*	↘	↘		(↘)	*0*			↘
D2	*Inh*	↘	↘		(↘)	*0*			↘
TK	*Facil.*				↘		↘	↗	↗
NPY	*Inh*								*0*
SOM		*0*	*0*		*0*		↗		↘
NT		*0*	*0*		*0*				↗

The table summarizes the results of a number of studies (see text). The effects of different transmitters and receptors on different targets are listed in the columns on the right. Gray background color indicates receptors known to be activated endogenously during fictive locomotion. The presynaptic actions can be targeted to sensory afferents, excitatory or inhibitory interneurons, and descending reticulospinal axons. Different transmitters have selective actions on different cellular targets (I, presynaptic inhibition; F, facilitation). The locomotor network phasically modulates, in each cycle, the synaptic transmission from sensory afferents and interneurons. The modulation of HVA_{Ca}, LVA_{Ca}, K_{Ca}, and K^+ and NMDA channels is indicated with a downward arrow for depression and an upward arrow for facilitation. Again, the effects may be specific to particular cell types. Finally, the effects on the network level have been studied on the background of locomotor activity (arrows relate to locomotion burst frequency) and in related modeling experiments. 5-HT, 5-hydroxytryptamine (serotonin) receptor; D_2, type 2 dopamine receptor; HVA, high-voltage-activated; mGluR, metabotropic glutamate receptor; NPY, neuropeptide Y; SOM, somatostatin; NT, neurotensin; TK, tachykinin.

extent, determined by the actions of these modulatory systems, which help the network adapt to different behavioral challenges. In the lamprey (Table 1), the molecular targets of several modulators have been identified. Since intrinsic network function and behavior is also well understood, it is possible to estimate the effect of modulation of a target gene on the actual motor behavior and thus bridge the gap from gene to behavior (see Grillner, 2003).

Planning, Prediction, and Corrections

The decision to perform a given motor behavior is often triggered by events in the surrounding world—the appearance of prey or a foe, for example. Moreover, when moving through the terrain or on a street, there are obstacles that need to be circumvented in a predictive fashion (see Drew et al., 2004). This type of predictive command, or feedforward control, is critical for practically all creatures and is an important part of the general strategy of neural control (see also below).

Sensory information is equally important in reacting to unpredicted perturbations that occur during the actual performance of a movement, like slipping on an oily surface. Due to the inherent delays in biological feedback loops (e.g., Grillner, 1985), there is little time for corrections during the same phase of very fast movements (eye saccades or gallop movements). During slower movements, on the other hand, there can be sufficient time for corrections. Sensory control mechanisms are an inherent part of the design of certain CPGs, and they help to determine the cessation of inspiration during breathing (von Euler, 1981) and the end of the support phase during slow locomotion (Duysens and Pearson, 1980; Grillner and Rossignol, 1978b; Rossignol et al., 2006). There also are sensory mechanisms that affect the overall amplitude of the output to individual muscles (Stein and Daniels-McQueen, 2002). In only one case, the lamprey locomotor system, the synaptic interactions between the stretch receptor neurons that sense the ongoing locomotor movements and the CPG interneurons have been identified (Viana Di Prisco et al., 1990; see Grillner, 2003). The sensory input produced by such perturbation can effectively adapt motor patterns and even entrain CPG activity.

Importantly, knowledge of the organization of spinal sensory control mechanisms and the CPGs of the locomotor system (Grillner, 1973, 1985; Rossignol et al., 2006) has led to the establishment of a form of "walking therapy" for patients with partial spinal cord injury (Behrman et al., 2005; Wernig et al., 1995; see Grillner, 2003). This strategy is based on the reactivation of dormant spinal locomotor circuits. Patients that have become wheelchair bound, can be trained on a treadmill to recover locomotor faculties. This type of training results in locomotor-like movements that provide a rough replica of the sensory input that would normally occur during a step cycle. Given a significant period of training, some patients recover the ability to support the body and walk, usually with assistance of a cane or a walker—a very significant improvement in the quality of life. As in other mammals, such training protocols are thought to result in an activity-dependent plasticity in the sensory components of the locomotor circuitry and in the central locomotor networks.

Phasic Presynaptic Modulation of Synaptic Efficacy of Both Sensory Afferents and Intrinsic Network Components

A phasic presynaptic GABAergic inhibitory action on dorsal root afferents during locomotor activity has been documented in many vertebrate and invertebrate species (see El Manira and Wallén, 2000; Rossignol et al., 2006). Different classes of afferents are inhibited presynaptically in different phases of the step cycle. The efficacy of the synaptic transmission from different sensory afferents is therefore gated during the step cycle and is more efficient at one particular phase of the movement.

The lamprey is the only vertebrate species in which a phasic presynaptic action in the axonal terminals of premotor interneurons has been documented (Alford et al., 1991). Recordings from axonal branches of both network interneurons and sensory afferents show that during each ipsilateral locomotor burst, axons are phasically depolarized through both $GABA_A$ and $GABA_B$ receptors. Since sensory axons have a comparatively negative membrane potential, $GABA_A$ receptor activation causes depolarization and increases membrane conductances, thereby shunting the amplitude of the action potential and reducing transmitter release (Cattaert et al., 2001; El Manira et al., 1997). The $GABA_A$ receptor-mediated action is fast and contributes to a phasic regulation of synaptic efficacy, whereas slower metabotropic modulation by peptides, glutamate, and $GABA_B$ receptors acts in a tonic fashion or during slow burst activity. Not only excitatory but also inhibitory synaptic transmission to motor neurons and network interneurons is reduced during the burst (Alford et al., 1991). The axons of premotor interneurons in other vertebrates have not been studied successfully, and it is therefore possible that such presynaptic actions are common in other systems and at different levels of the CNS. Descending corticospinal axons may also be subject to presynaptic modulation (Jackson et al., 2006). In the stomatogastric system, analysis of a more elaborate presynaptic modulation has been detailed, in which chemical presynaptic action is combined with electric gap junctions (see Nusbaum and Beenhakker, 2002).

Visuomotor Coordination of Cortical and Spinal Processing

The different CPGs involved in the most basic aspects of our behavioral repertoire—walking, posture, breathing, chewing, swallowing—can be recruited and operate to perfection in mammals that lack their cortex (Bjursten et al., 1976). However, locomotor movements that require visuomotor coordination with a precise foot placing—like walking up a ladder, when each foot must be accurately placed on each rung—is difficult not only in the decorticate state but also after transection of the corticospinal tract (see Georgopoulos and Grillner, 1989). During this type of "precision walking," neurons in motor cortex become strongly activated in precise phases of the movements (Beloozerova et al., 2003; Drew et al., 2004). The same neurons are also activated during reaching tasks. These corticospinal neurons are thus involved in the precise placement of the limb, whether in locomotion or other motor tasks. The accurate placement of the foot during locomotion in complex terrain can best be considered as a dynamic reaching movement superimposed on the locomotor movement itself (Georgopoulos and Grillner, 1989).

Let us now consider the response patterns of neurons in motor cortex during reaching tasks in primates. Essentially, they respond to the direction of movement with a broad tuning curve with a maximal response in one direction and a reduced activity during movements in the opposite direction (Georgopoulos et al., 1986). If a population of cells is considered, the population vector defines with high accuracy the direction of the upcoming movement. This strategy seems attractive, and the motor cortex is thus concerned with the direction of the movement toward a target. This is an important but at the same time puzzling finding. Only a small population of corticospinal cells project monosynaptically to motoneurons in the cervical spinal cord and are thus linked to specific sets of muscles (Dum and Strick, 2002), the large majority instead targets spinal interneurons.

Moreover, a reaching movement in a given direction will use different muscle groups depending on the orientation of the arm at the onset of the movement—take for instance an upward movement in the wrist or elbow, which will involve different muscles depending on whether the palm or the dorsum of the hand is directed upward. It would hardly be possible to achieve this by hardwired projections to specific motoneurons/muscle groups, whether via direct corticospinal or indirectly via rubro- or reticulospinal projections. Most researchers discuss the cortical commands as if they were achieved by the monosynaptic corticomotoneuronal projection. These direct projections are weak, however, and mainly concerned with the most distal muscles. How do we resolve this paradox? I raise the possibility that corticospinal di- or multisynaptic projections can be gated at the spinal level to different target motoneurons, depending on the initial orientation of the limb.

Are Commands from Motor Cortex Gated at the Spinal Level?

The fact that the overwhelming majority of corticospinal neurons project onto interneurons of the spinal cord may add necessary flexibility. If so, how can this be achieved? The di- or multisynaptic corticospinal signals to motoneurons must, in this case, be channeled through separate pools of interneurons to target different, even antagonistic muscle groups, depending on the orientation of the arm or the phase of the movement. Let us scrutinize the indirect evidence available that supports the viability of such a proposition, i.e., that a given corticospinal neuron, activated in conjunction with a movement in a certain direction, could have its motor effects gated to different motoneurons/muscles, dependent on the orientation of the limb or the phase of an ongoing movement (see Figure 10). This would require that a "sensory body scheme" is available at the spinal level in which the actual position of the limbs in relation to the body is continuously updated. Information based on the continuous input from a variety of afferents (muscle, joints, ligaments, and skin) and from efference copy information is actually known to be available. Both are integrated at the spinal level and are sufficient to

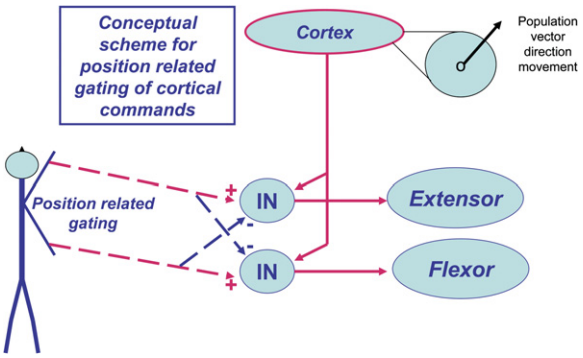

Figure 10. Spinal Position-Dependent Gating of Corticospinal Commands—A Hypothesis

A gating of the motor effects to flexor and extensor muscles dependent on the position of the affected limb has been demonstrated previously (see text). It is proposed that such gating effects could also apply to the corticospinal and other forebrain commands, most of which are mediated by interneurons that also receive sensory input. This would resolve the apparent paradox that neurons in motor cortex code for the direction of movement, although different muscles would have to be activated dependent on the orientation of the limb (see text). IN, interneuron; red, excitation; blue, inhibition.

provide reliable information about the orientation of the limb (Bosco and Poppele, 2001).

There are several clear-cut examples of gating of motor effects at the spinal level that are induced by the position of the limb itself or by the motor program being executed.

- During both standing and locomotion, an identical sensory stimulus can activate different combinations of muscles, depending on whether the limb is in a forward or a backward position. For instance, a given sensory stimulus to one limb will elicit opposite motor effects on contralateral limb muscles dependent on whether the contralateral limb is in a flexed (forward) or extended (backward) position. In the first case, extensors are activated on the contralateral side, and in the second case, flexors (Grillner and Rossignol, 1978a). Clearly, sensory information regarding limb position is able to gate motor effects elicited by sensory stimulus, such that interneurons activating flexors become activated in one case, and those activating extensors in the other. This gating effect is produced at the spinal level and is due to the sensory information about limb position available at the instant of stimulation—we are thus not dealing with a feedback mechanism.
- A similar finding with even more elaborate spinal processing has been provided by Fukson et al. (1980). A spinal frog can wipe away an irritant from the distal part of its forelimb with the hindlimb with great accuracy, regardless of the initial orientation of the forelimb. The forelimb can be placed in a forward or in a backward position in relation to the body, with stimulation of an identical spot on the distal skin. The same sensory stimulus to the skin, but with different spatial coordinates in relation to the body, elicits a different hindlimb motor command that results in an accurate wiping movement to different points in space. In effect, this shows that sufficient sensory information is available in the spinal cord to permit the orientation of the forelimb to drive the appropriate wipe motor command. Thus there is a body scheme available at the spinal level that can serve to gate appropriate motor commands.
- During ongoing locomotion, an identical sensory input applied to the paw may activate flexors in one phase of the movement but extensors in another. This is a functionally meaningful response pattern: flexors will be activated during the swing phase, and extensors when the limb supports the body. This phase-dependent gating of the sensory input is performed by the spinal locomotor CPG at an interneuronal level (Andersson et al., 1978; Forssberg et al. 1977) and has been referred to as a phase-dependent reflex reversal.
- Finally, there is extensive and powerful convergence of segmental afferents and corticospinal neurons on spinal premotor interneurons (see Lundberg, 1979; Lundberg et al., 1962). This convergence allows for a potential gating of corticospinal effects at the spinal level, dependent on the sensory input that accompanies a given limb position.

At the spinal level, the gating of motor effects can be induced by the position of the limb itself or by the resultant motor program. An illustration of how sensory afferent input in a forward position can facilitate one group of interneurons and inhibit the antagonist group, while the converse would be true in the backward position, is shown schematically in Figure 10. The cortical command will, depending on limb position, be gated to one or the other group of motoneurons. I propose that this spinal position-dependent information can be used to gate motor commands to the appropriate muscle groups, such as the corticospinal di- or multisynaptic signals to the appropriate muscle group, whether flexor or extensor (Figure 10). A spinal gating strategy of this type would simplify the task for the cortical command. It would also resolve the apparent paradox that the overwhelming majority of corticospinal neurons in motor and premotor cortex respond to the direction of movement regardless of which muscles are to be used in a given movement. Cortical commands may therefore need only to concern themselves with the direction of the movement (Georgopoulos et al., 1986).

In a similar way (Figures 3C and 8), the brainstem locomotor command regions activate locomotor CPGs, whereas the coordination of hundreds of different muscles is handled at the spinal level. This is, in principle, an effective control strategy through which basic elements of coordination are delegated to the spinal level.

An Overall View

Central motor pattern generators have provided the first deep insight into the *circuit doctrine.* Their existence implies, in turn, that parallel principles might be encountered in perceptual and cognitive networks. In the case of motor programs, we see that the nervous system of a given individual or species is equipped with a species-specific "motor infrastructure," a number of preassembled circuits in the form of unit CPGs that can be

recruited into action and generate the varied range of motor behavior. These circuits have significant flexibility so that sensory information can interact with CPGs in a variety of ways. The dynamic information that concerns limb position available at the level of spinal interneurons may serve to channel or direct sensory signals and also signals from the forebrain to the appropriate group of motoneurons. Knowledge of the organization of the spinal sensory input and locomotor CPGs (Grillner, 1985) has also led to clinical applications, with establishment of a form of "walking therapy" for patients with partial spinal cord injury (Behrman et al., 2005; Wernig et al., 1995).

CPGs can be constructed from a limited number of molecular and cellular components. Nevertheless, a major challenge for the future is to understand how motor behaviors are generated at the molecular, cellular, and synaptic level—that is, an understanding at the microcircuit level—the interface between neurons and global brain functions (Grillner and Graybiel, 2006). Two approaches will prove essential. One will combine developmental, molecular, genetic, and neurophysiological approaches. The other will rely on comparisons between animals of different complexity—from lamprey and zebrafish to amphibians and mammals—to obtain crucial comparative insights.

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