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Invertebrate Central Pattern Generation Moves along

Review

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Central pattern generators (CPGs) are circuits that generate organized and repetitive motor patterns, such as those underlying feeding, locomotion and respiration. We summarize recent work on invertebrate CPGs which has provided new insights into how rhythmic motor patterns are produced and how they are controlled by higher-order command and modulatory interneurons.

Introduction

Although recent years have seen remarkable advances in both cellular and systems neuroscience, we still have only a rudimentary understanding of how cellular mechanisms give rise to circuit function, and even less understanding of how circuit dynamics give rise to systems-level and cognitive behaviors. There has been a resurgence of interest in central pattern generators (CPGs), the central circuits that give rise to organized and repetitive movements [1,2], because the outputs of these circuits are easy to measure, and their functions important to the animal. CPGs therefore provide ideal test-cases for assessing the consequences of genetic and molecular manipulations [3–6]. Moreover, the growing recognition that brain rhythms are widespread has also led to increased interest in the general mechanisms underlying rhythm generation. Work on invertebrate CPGs with small numbers of easily identified neurons has been critical in establishing many general principles relevant to the organization of CPGs and other circuits in the brain. In this review, we focus on recent work using invertebrate CPGs that adds to our understanding of how circuits generate behavior.

What Are Central Pattern Generators?

Rhythmic movements such as breathing, walking, swimming and feeding are produced by central circuits that generate rhythmic motor patterns even in the absence of timing cues from sensory neurons or other extrinsic inputs [1,2]. The most direct demonstration that motor patterns can be centrally generated without requiring sensory input comes from the large number of preparations that generate fictive motor patterns when the preparations are removed from the animal and studied *in vitro*. In the case of many invertebrate preparations, the correspondence between these fictive motor patterns and those generated by the behaving animal is obvious, thus creating confidence that mechanisms studied *in vitro* are relevant to the generation of behavior [2].

The following questions recur frequently in the study of CPGs: Which neurons are part of the CPG? What are the intrinsic membrane properties and connections of these neurons that account both for their rhythmicity and the specific timing of activation of the component neurons? How do sensory neurons alter or gate the CPG output? How are the CPG motor patterns activated, inhibited, or modified by modulatory drive? How are complex behaviors produced by coupling multiple oscillator subcircuits? To what extent can different behaviors be produced by reconfiguration of the same circuits? How is the CPG output transformed by the periphery into movement? What role does activity play in the development of central pattern generating circuitry and behaviors? Recent work using invertebrate preparations has illuminated each of these questions.

Characterization of CPG Neurons and Circuits

It is not an accident that preparations with easily identifiable neurons and robust motor patterns have dominated studies of CPGs. After years of painstaking work with conventional electrophysiological methods, genetically expressed fluorescent markers [7] and novel optical methods [8–10] are becoming useful tools for further locating and identifying neurons that participate in CPGs. Historically, the criteria for deciding when a neuron is part of a CPG included demonstrating that the neuron was active in time with the rhythm, and that perturbing its activity could entrain or reset the rhythm (to distinguish CPG neurons from motor neuron followers). However, these criteria are not always helpful in deciding whether or not neurons are part of a CPG, as sensory neurons may meet both of these criteria without being necessary for the generation of the motor pattern. Today, it seems more productive to try to understand how a given circuit works, rather than falling into the trap of arguing where to draw the boundaries between the CPG neurons and their sensory and extrinsic partners in behavior.

In general, rhythmicity in a circuit can arise either from neurons with the ability to generate rhythmic bursts in isolation, or as a consequence of circuit interactions (Figure 1A). We shall consider these mechanisms in the sections that follow.

Reciprocal Inhibition and 'Half-Center Oscillators'

It has long been known that reciprocal inhibition between functional antagonists can produce alternating discharges in neurons that produce alternating activity in antagonistic motor neurons [11–14]. An important feature of such 'half-center oscillators' is that it is possible to obtain sequences of alternating bursts of activity from reciprocal inhibition, even when the isolated neurons are not themselves capable of

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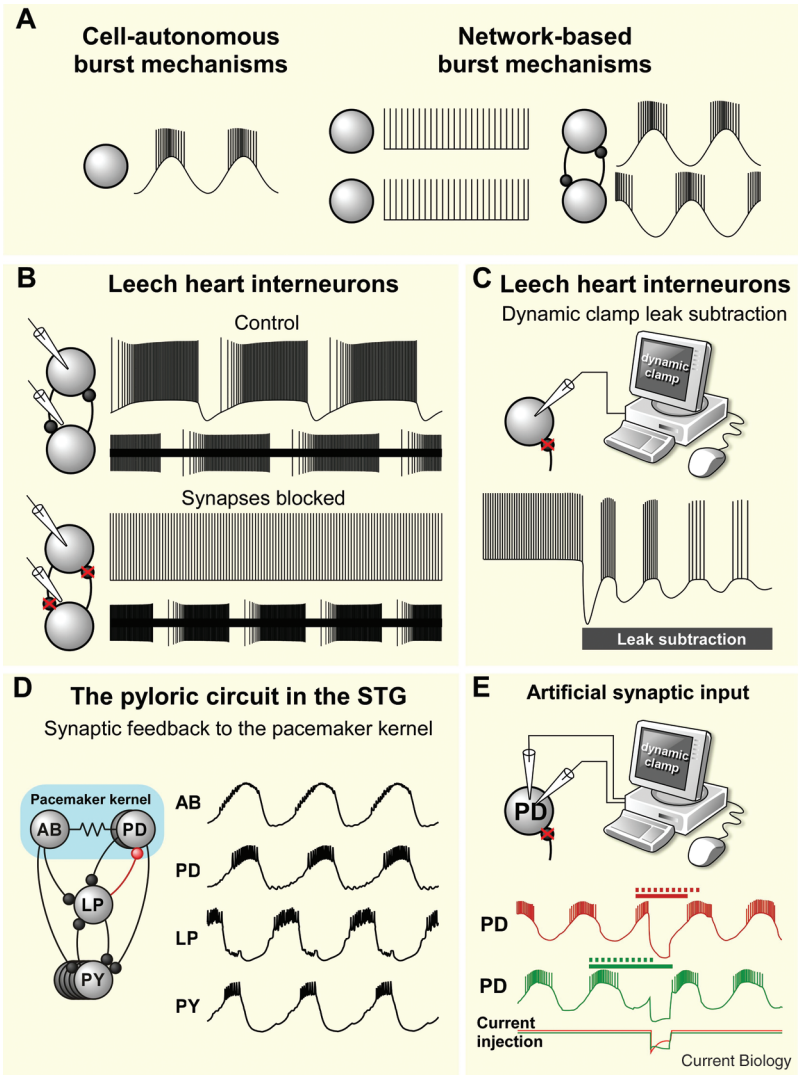

Figure 1. Mechanisms of burst generation.

(A) Rhythmic network activity can result from intrinsic bursting properties of neurons in the network. Such neurons generate bursts in the absence of synaptic interactions (left). In other cases, rhythmic activity is the consequence of synaptic interactions between silent or tonically spiking neurons (right). (B) Rhythmic activity in the leech heartbeat system was thought to arise from mutual inhibition of bilateral pairs of interneurons, because intracellular recordings (upper traces) show that these neurons fire tonically in the presence of synaptic blockers. However, rhythmic activity persists in the absence of synaptic interactions when a non-invasive extracellular recording method is used (lower traces). (C) The loss of bursting activity in leech heart interneurons with intracellular recordings is the result of an increased leak conductance. When this leak conductance is subtracted using dynamic clamp, bursting activity resumes. (D) The pacemaker kernel of the triphasic pyloric rhythm (right) in the lobster *Homarus americanus* receives inhibitory feedback from a single LP neuron (left). (E) The effect of this feedback depends on when in the cycle LP is active. Injecting artificial synaptic input into the PD neuron results in either advance (red trace) or delay (green trace) of the pacemaker burst depending on the timing of the synaptic input. The solid line above the PD trace shows the actual onset of the PD burst subsequent to current injection, while the dotted line indicates the predicted timing of the PD burst in the absence of current injection. (B,C) reproduced with permission from [26]. (E) reproduced with permission from [34].

bursting [14,15]. In both *Clione* swimming [16] and the leech heartbeat system, reciprocal inhibition has been considered the major mechanism underlying the generation of rhythmic movements.

The leech heartbeat is coordinated by a simple circuit at whose core is reciprocal inhibition between pairs of heart interneurons (HN cells) that project to heart motor neurons in almost all segments, producing peristaltic/synchronous contractions that drive blood flow. The voltage-gated channels present in the HN cells and their synaptic interactions have been painstakingly analyzed [17–22]. This work culminated in a series of biophysical models of the leech heart half-center oscillator [23–25] which incorporated voltage-clamp data on the conductances found in the HN neurons, and on the synapses between them. The initial models drew on data from intracellular recordings which showed that HN cells fired tonically when pharmacologically isolated [19,20]. Therefore, the rhythmic alternation of activity in the two HN neurons was thought to result from the reciprocal inhibition between them, in a classic half-center oscillator [11] in which the oscillation arose as an emergent property of the interactions between the synaptic connections and the membrane currents of the tonically active neurons.

This conclusion has been revised as a consequence of a new study [26] in which extracellular recordings were made from the HN cells, simply by placing the electrode against the soma (Figure 1B). With this less-invasive technique, it has been shown that isolated HN cells typically burst endogenously, rather than fire tonically. This suggests that even a small leak current introduced by microelectrode impalement causes the cells to undergo a transition from endogenous bursting to tonic firing. The importance of the leak conductance was studied using models [25,26]. In a single HN model neuron, there is only a very small regime in which bursting is found. Even minor impalement damage, raising the leak conductance, could be sufficient to move a bursting cell into the tonic regime, as was shown by using the dynamic clamp to slightly decrease the leak (Figure 1C). However, when the HN model neurons were coupled synaptically, the resulting model network had

a much larger oscillatory regime, and electrode-induced leaks of reasonable magnitude did not disrupt bursting. Thus, in the animal, the HN neurons seem to be 'just capable' of bursting in isolation, but the robust and stable bursting seen when they are coupled is largely a function of the reciprocal inhibition between them. Presumably the fragility of the burst mechanism in the isolated HN neurons makes it easier for each of the neurons to entrain the other, thus avoiding problems that could occur in synchronizing strong oscillators with different intrinsic periods. This is an example of a CPG that has multiple, overlapping mechanisms for producing oscillations, a general principle that emerges from studies of many CPGs.

Pacemaker-Driven CPGs

The pyloric rhythm of the crustacean stomatogastric ganglion (STG) is a pacemaker-driven motor pattern [27]. The pyloric rhythm is characterized by a triphasic sequence of activity in the Pyloric Dilator (PD), Lateral Pyloric (LP) and Pyloric (PY) neurons (Figure 1D), which alternately dilate (PD phase) and constrict (LP phase followed by PY phase) the pylorus. The dilator phase is generated by a three-neuron electrically coupled pacemaker kernel consisting of the two PD neurons and a single Anterior Burster (AB) interneuron, which together inhibit the other neurons of the pyloric rhythm. The LP and PY neurons in turn fire on rebound from inhibition. Work over the past twenty-five years has addressed a series of issues about the control of frequency and phase within the pyloric discharge. These questions can be addressed separately, because frequency and phase can be regulated independently [28].

Frequency regulation of the pyloric rhythm can, in principle, be achieved by altering the frequency of the pacemaker kernel itself, or indirectly via the single feedback connection from the pyloric circuit, an inhibitory synapse from the LP neuron to the PD neurons. Numerous neuromodulators directly influence the frequency of the pacemaker kernel neurons (for example [29–32]). The role of the feedback synapse in frequency control has been much more confusing, and the strong LP inhibition of the PD neurons can either have a considerable or little effect (Figure 1E) on the pacemaker frequency, depending on when the LP neuron is active in the cycle [29,33–36] because of the shape of the phase-response curve of the PD neuron's response to inhibitory inputs [34].

Understanding phase regulation in the pyloric rhythm has been a difficult process. The time at which the LP and PY neurons start to fire after the pacemaker kernel burst depends on both the kinetics of the synaptic potentials evoked by the AB and PD neurons and the intrinsic membrane currents in the LP and PY neurons [28,37–40]. Therefore, modulation of either of these properties can alter the phase relationships at which the LP and PY neurons fire [28,41,42]. Much more difficult to understand is the observation that over a fairly substantial frequency range, the pyloric rhythm can maintain approximately constant phase relationships [28,43–46]. This finding comes from experiments in which large numbers of control recordings from different preparations were analyzed [43] and from experiments in which the frequency of the pyloric rhythm was altered by current injection directly into the AB or PD neurons [44,45].

Until recently, the finding of phase maintenance over a substantial frequency range was quite puzzling, because the fixed time constants of synaptic and membrane currents would, in principle, lead to fixed delays, and hence variable phases, as the frequency of the rhythm varies (Figure 2A). New work has now provided insight into how constant phase can be maintained [47–50] as a result of synaptic depression and the kinetics of inactivation of the transient outward potassium current, I_A. I_A influences the delay to firing after hyperpolarization, causing the delay to scale with the strength and duration of hyperpolarization, and thus might be expected to contribute to phase invariance [51] (Figure 2B). Many pyloric network synapses show synaptic depression [52], which may aid phase maintenance by weakening synapses during a fast rhythm, and allowing them to remain strong during a slow rhythm (Figure 2C). Recent theoretical work suggests that synaptic depression could promote phase invariance, and that I_A would enhance this effect [48–50] (Figure 2D).

When isolated from their synaptic drive, the LP and PY neurons fire bursts with irregular periods and exhibit chaotic dynamics — their voltage trajectories are irregular, and this irregularity is *not* due to thermal or other noise sources [53–55]. It is not clear what functional role, if any, chaotic dynamics might play in the pyloric network, because the LP neuron's irregular bursts are regularized by periodic inhibition, of the kind LP receives during the ongoing pyloric rhythm [54].

Intersegmental Coordination

In segmented animals, many CPGs drive behaviors in which each segment does more-or-less the same rhythmic movement, but these movements must be coordinated between segments. Such behaviors have an inherent 'modularity' (each segment being a module), and in general this modularity is reflected in the neural circuits that generate them. In principle, the outputs of segmental CPGs could be coordinated biomechanically, by sensory feedback, or by central coordinating systems. Each of these mechanisms is likely to play a role to a greater or lesser extent in different systems. At one extreme, there is the crayfish swimmeret system, in which the appropriate phase lags between segments are maintained in the absence of sensory feedback [56–58]. At the other, there is the stick insect, in which central coordination seems inadequate to entrain the different segments (or even different joints), and sensory feedback provides most of the information necessary to do so [59–63]. In between, there is the leech swim CPG, in which the phase lags observed *in vitro* are approximately two-thirds of those found *in vivo* [64] (Figure 3). Differential reliance on cycle-by-cycle sensory feedback may reflect differences in the control requirements for each behavior. For example, swimming involves movement through a relatively constant

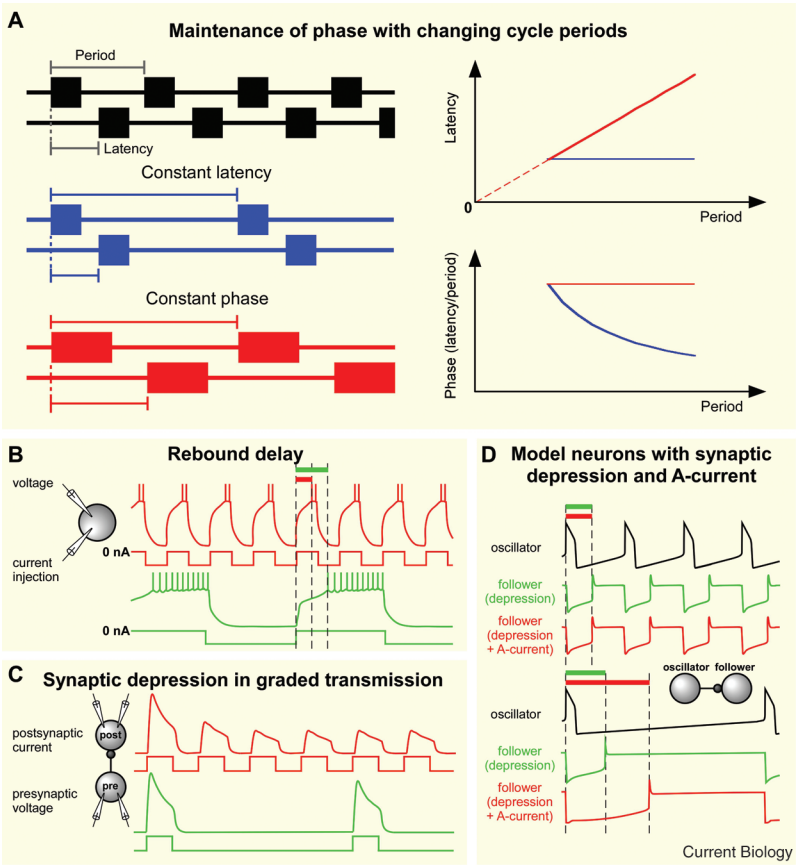

Figure 2. Phase maintenance in rhythmic networks.

(A) Latency may stay constant (blue) or scale proportionally to the change in period (red). If the latency stays constant, phase (latency/period) decreases with increasing cycle period. If the latency changes proportionally with the period, the phase stays constant. (B) Rebound delay that increases with increasing period in a lobster STG neuron. (C) Graded inhibitory synapses (recorded in voltage clamp as outward currents) in the pyloric circuit show synaptic depression. Consequently, synaptic strength during rhythmic activity depends on the cycle period. (D) The consequences of cycle period for synaptic strength in a simple oscillator-follower model with a graded inhibitory synapse. A combination of synaptic depression and A-type potassium current mimics phase maintenance of the follower neuron rebound (red traces). A-current alone has no effect (not shown) as cycle period increases, and synaptic depression alone (green) has a much smaller effect than both mechanisms combined (top vs. bottom traces). (B) reproduced with permission from [51]. (C) reproduced with permission from [35]. (D) reproduced with permission from [50].

medium, whereas walking must accommodate an often variable substrate.

The problem of phase invariance also arises in the context of intersegmental coordination, in a somewhat different form than in non-segmental CPGs. Segmental behaviors typically involve the maintenance of an approximately constant phase difference between the oscillations in neighboring segments, even in the face of changes in the common oscillation frequency [65]. In the crayfish, there is a phase difference of 90° between neighboring segments, with posterior segments leading [58]. In leech swimming, the phase difference is ~20° (measured kinematically), with anterior segments leading [64,66] (Figure 3A). In leech heartbeat, the phase differences between segments vary down the body, but they are still maintained as frequency varies [67,68]. Thus a key question for all of these circuits is how they manage to maintain constant phase relationships over a range of frequencies.

Skinner and Mulloney [57,58] developed a semi-realistic model of the crayfish swimmeret system that maintained the appropriate 90° phase lags over a realistic range of frequencies. In the model only a particular pattern of connectivity yielded the appropriate phase lags, so the model made predictions about the signs of various intersegmental synapses. In subsequent work Mulloney and coworkers have refined this model [56], and elucidated the intersegmental coordination circuitry in an attempt to test the model predictions [69–71].

Recent work on leech swimming has focused on understanding the role of sensory feedback in generating appropriate intersegmental phase lags. An isolated leech nerve cord can generate fictive swimming, but the phase lags between motor bursts in neighboring segments are unrealistically small (Figure 3A,B). Yu *et al*. [64] severed the leech nerve cord in otherwise-intact leeches, and found that these leeches still swam in a coordinated fashion, although the intersegmental phase lags were altered (Figure 3C). Sensory information is fed to the swim CPG by the ventral stretch receptor (VSR), a segmentally repeated stretch receptor, found in the ventral longitudinal muscles [72] which makes both direct and indirect connections with the CPG neurons [73]. Cang and Friesen [74] showed that by stimulating a VSR they could retard or advance the phase of motor neuron firing in that segment, depending on the phase of VSR stimulation. This work resulted in a model of intersegmental coordination in the leech swim CPG [75] which accounted for the relatively small phase lags in the isolated nerve cord. When the model was extended to include the body wall and stretch receptors, the phase lag between segments lengthened, as was found experimentally. The authors adjusted the model parameters to fit the above data, and then tested the model's fit to novel data. Specifically, they simulated cutting the connective at mid-body, but leaving the leech body wall and musculature intact and found a large increase in

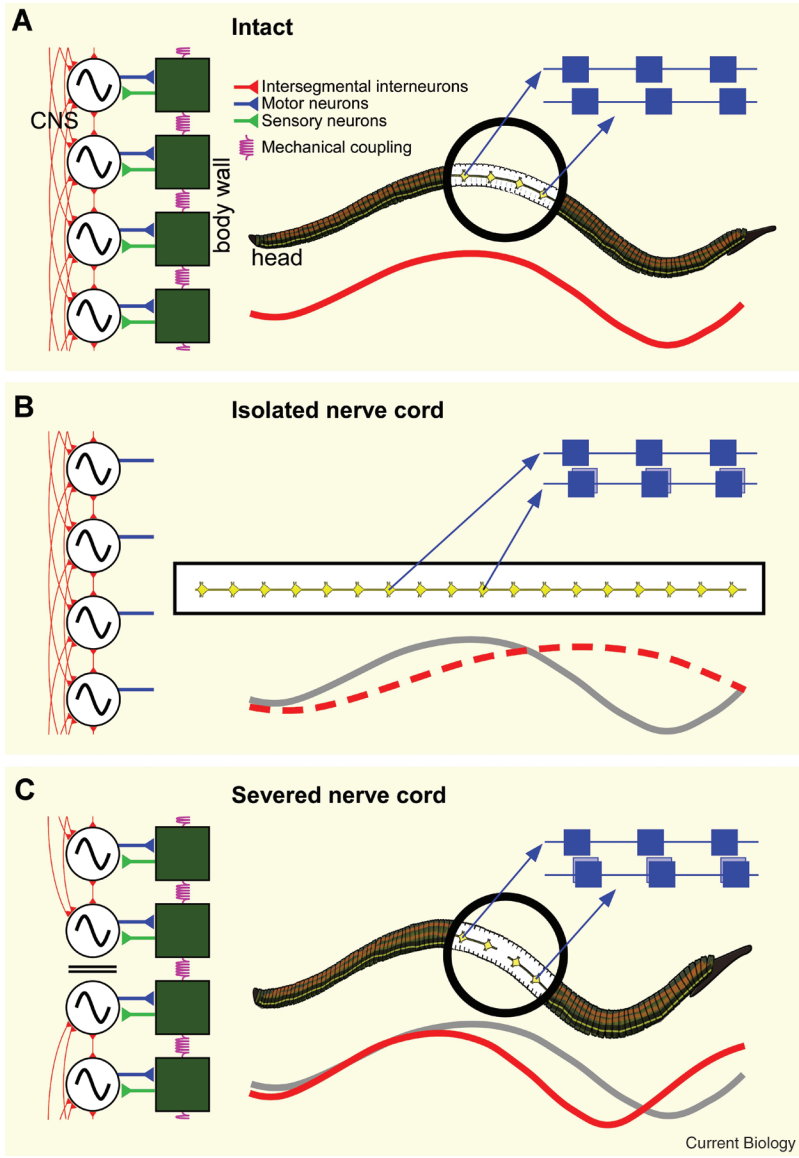

Figure 3. Effect of sensory feedback and body/medium dynamics on intersegmental coordination of leech swimming.

(A) Normal leech swimming. The diagram at left shows factors influencing intersegmental timing in the intact leech. The blue inset shows *in situ* extracellular recordings from motor neurons innervating swim muscles (for recordings three segments apart). Phase lags between motor neurons in neighboring segments are ~15° [64,191]. A leech is shown, from the side, in the normal swimming posture. A swimming leech maintains a wavelength of approximately one body length, as shown. Thus the 18 body segments that participate in swimming maintain per-segment phase lags of ~20° [64]. (The discrepancy between the motor neuron phase lags (~15°) and the body phase lags (~20°) is presumably due to intersegmental mechanical interactions of the body wall and fluid medium [75].) The red line shows the approximate shape of the leech body. (B) Isolated nerve cords display shorter intersegmental phase lags. The diagram at left shows the absence of sensory feedback in the isolated nerve cord. In this preparation intersegmental phase lags, as measured in the motor neurons, are reduced to ~10° (blue inset) [64,191]. The light blue motor neuron recording shows where the motor neuron burst would be in the nervous system of an intact leech. The dashed red line shows a fictitious body shape, based on the reduced intersegmental phase lags in this preparation. The fictitious body shape makes up only 2/3 of a wavelength, because the motor neuron phase lags in an isolated nerve cord are ~2/3 (10°/15°) of those found in the intact leech. The gray line shows the normal leech body shape. (C) Leeches with a nerve cord transected at midbody show longer intersegmental phase lags across the cut, and express more than a single wavelength over the body length. The diagram at left shows the effects of cutting the nerve cord at mid-body on the intersegmental synapses. The leech drawing and red midline show that the kinematic phase lags near the cut are lengthened in this condition, to ~25° per segment [64]. Similarly, the blue inset shows that the phase lags between the motor neuron bursts near the cut are lengthened, to ~20° per segment [64].

phase lag between the front and back halves of the animal, consistent with experimental findings.

The segmental coordination of leech heartbeat is achieved differently than in crayfish swimmeret beating or leech swimming. Rather than having a CPG in each segment, the leech heart is driven by a CPG that resides only in the first seven segments of the body. Recent work has examined the coordination between the half-center oscillators in G3 (ganglion 3) and G4. When they are isolated from the rest of the nervous system, the phase lag between these two oscillators varies considerably from animal to animal, although it is stable from cycle to cycle [76–78]. To investigate the sources of this phase difference, Hill *et al.* [79] constructed a model of the coupled segmental oscillators that predicted that the source of the phase difference between G3 and G4 was the difference in the intrinsic frequency of the segmental oscillators. It further predicted that the frequency of the coupled system would be equal to the frequency of the faster segmental oscillator. These predictions were tested by blocking the connection between the two ganglia, and were found to be accurate [76–78]. Thus the phase differences in the core leech heartbeat CPG are primarily due to differences in the frequencies of the segmental oscillators. A new model, which includes the spike-frequency adaptation seen in the coordinating fibers and asymmetry in connectivity, was better able to explain certain asymmetries in the ability of G3 to entrain the system, when compared with G4 [80].

Stick insect walking provides an interesting contrast to the systems described above. In addition to intersegmental coordination, insect walking also involves issues of *interjoint* coordination. Each thoracic ganglion in the stick insect controls a pair of legs, and each leg has three main joints: the thoracocoxal (TC) joint, the coxa-trochanteral (CTr) joint, and the femur-tibia joint (FTi). When deafferented and properly stimulated, a single thoracic ganglion can generate alternating bursts in the motor neuron pools subserving antagonistic muscles [62,63,81]. However, these alternating bursts display no interjoint coordination: the motor neurons innervating FTi joint extensors have no fixed phase relationship to those innervating CTr joint levators [63]. This suggests that, although there are individual CPGs for each joint, the coordination between joints is primarily generated by sensory feedback.

Some aspects of this sensory feedback have been elucidated. Signals from the femoral chordotonal organ (fCO), which reports the extension at the FTi joint, can cause the CPG for the CTr joint to switch from a levation phase to a depression phase [60,82]. Similarly, signals from the trochanteral campaniform sensillae (trCS), which senses load near the CTr joint, can switch the TC-joint CPG from protraction to retraction phase [59]. In both cases sensory information pertaining to one joint influences the CPG for another joint, thus lending itself to interjoint coordination.

Neuromodulation in Central Pattern Generating Circuits

It is common for researchers on vertebrate preparations to attribute global changes in the state of brain circuits to the action of single neuromodulators, such as dopamine and its roles in reward and addiction. This is despite the obvious presence of many neuromodulators in all brain areas, and the very large number of neurons that release cotransmitters. The temptation to assign global function to a single neuromodulator is obvious, but all work on the neuromodulation of CPGs in invertebrates demonstrates that circuit modulation is achieved, not by a single neuromodulator, but by many neuromodulatory substances and neurons, which together can reconfigure neuronal circuits to produce multiple outputs [1,2,83]. This principle is dramatically illustrated in the stomatogastric nervous system, in which at least 20 different substances are found in modulatory projections to the STG (Figure 4A), each of which evokes a different motor pattern [1,2,83–85].

CPG operation critically depends on the presence of neuromodulatory substances. The term ‘intrinsic neuromodulation’ has been used to refer to neuromodulators released by members of a central pattern generating network during the operation of the circuit, while ‘extrinsic neuromodulation’ has been used to refer to neuromodulation from sources outside of the circuit [86,87]. Neuromodulators shape circuit activity into potentially many different forms, presumably lending flexibility to the motor output for specific behavioral contexts [88]. In some cases neuromodulators may provide ‘fine tuning’ of cellular and circuit properties that alters an ongoing rhythm [89]. In other cases rhythmic activity depends on the presence of at least a baseline level of modulatory substances. Ultimately, to understand the operation of CPGs, we need to identify the complement of neuromodulatory substances that affect them, determine what the cellular and subcellular targets of each modulator are, and where, how and when they are released [83–85,89,90].

Identifying Neuromodulators

Neuromodulators include substances like glutamate, GABA, acetylcholine, biogenic amines, and neuropeptides. Additionally, many CPGs are also modulated by the gas nitric oxide [91–94]. Major progress in identifying the full complement of neuromodulators acting on CPGs has come with recent advances in mass spectrometry for neuropeptides [95–103]. These new methods have allowed the identification of the neuropeptides in single neurons [104] or small tissues and together with molecular techniques [105] have demonstrated that many neuropeptides are found as members of closely related peptide families.

Where, How and When Are Neuromodulators Released?

The same neuromodulatory substances are often released both as circulating hormones and from the terminals of modulatory neurons (Figure 4A). For example, in crustaceans, the pericardial organs are major neurosecretory structures that release many of the same substances found in modulatory neurons that enter the STG [100,106,107]. The full implications of using the same substances as circulating neurohormones and as local neuromodulators are not known, but presumably circulating hormones are ideally suited for the behaviorally relevant coordination of multiple target tissues, while local delivery allows more selective activation of one region of the nervous or muscular system.

Many modulatory projection neurons contain multiple cotransmitters including amino acids, amines, and neuropeptides [84,108] (Figure 4B) and project to multiple targets, both within a single ganglion or in several ganglia [84,109]. It then becomes critical to determine: the direct cellular targets for each neuromodulator; the dependence of cotransmitter release on the physiological activity of the modulatory neuron; the extent of convergence and divergence of modulator action on individual neurons within a given target circuit; and the extent to which a modulatory neuron may act to coordinate the activity of multiple circuits. Recent work has shed light on these issues.

An individual neurotransmitter/neuromodulator can activate multiple receptor types, and many neurons show multiple receptors to the same modulator/transmitter [110–113] (Figure 4C). Therefore, depending on the distribution of receptor types, the same substance can elicit different responses on different neurons. For example, in the STG, amines such as serotonin or dopamine elicit a variety of effects on synaptic strength and intrinsic conductances, including acting on two or more voltage-dependent conductances in the same neuron [29,114–117].

A given target neuron may have receptors to many different neuromodulators/transmitters, including

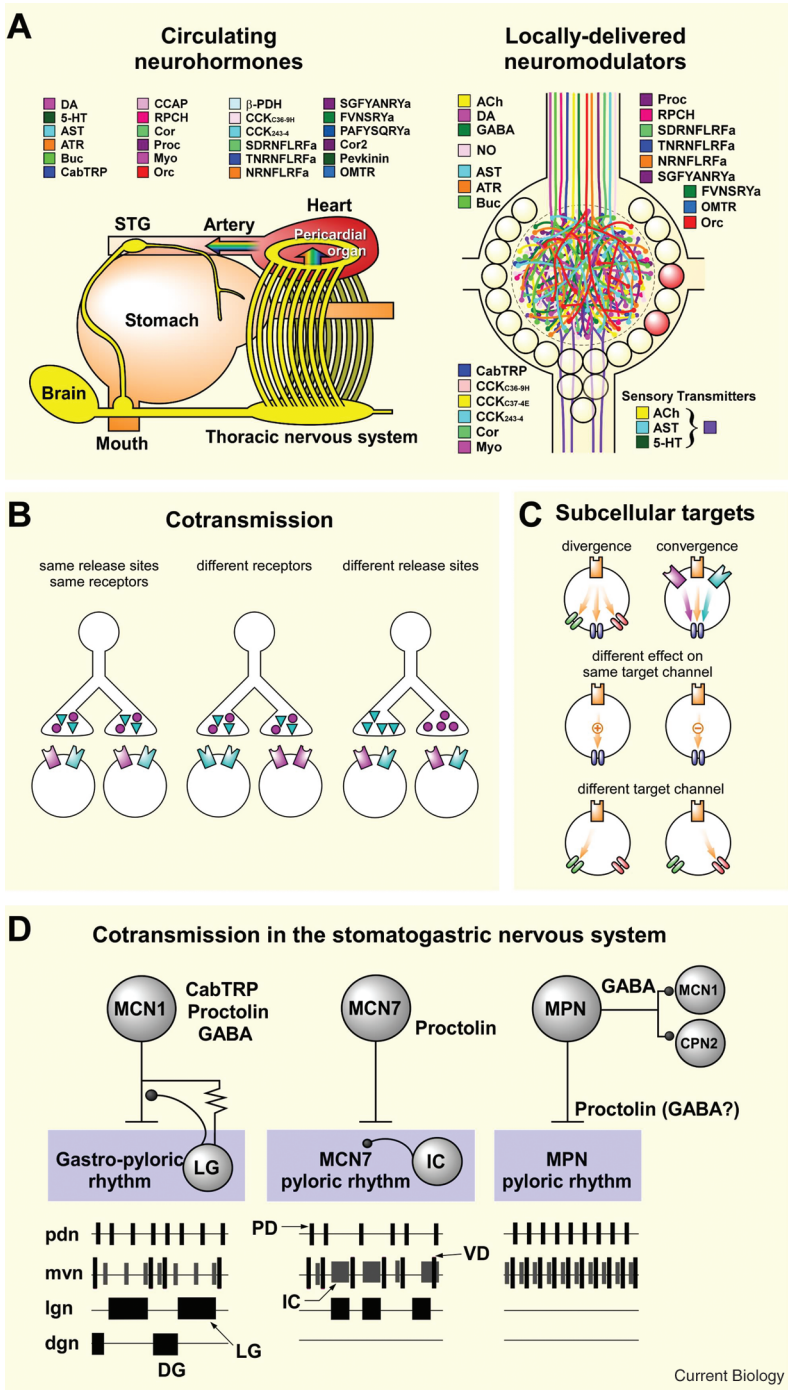

Figure 4. Neuromodulation.

(A) Modulation of the crab STG comes from circulating hormones released from the pericardial organs (POs) and other neurohemal release sites. Neuromodulatory inputs enter the neuropil of the STG from higher order ganglia and sensory neurons. (B) As a consequence of cotransmission, selective activation of different neurons may arise from different mechanisms. A neuromodulatory neuron may have spatially separated release sites. Target neurons at these sites may have receptors to only a subset of the transmitters released by the modulatory neuron, or the modulatory neuron may release only a subset of its modulators at a given release site. (C) Binding of a neuromodulator to its receptor on a target neuron may affect several subcellular targets (divergence). Receptors to different neuromodulators may affect the same subcellular target (convergence). Differential effects of neuromodulators on different target neurons within the CPG network can arise from different mechanisms. The same substance may have opposite effects on a subcellular target in different neurons, or it may affect different subcellular targets in different neurons. (D) Three proctolin-containing neurons in the crab STG evoke different motor patterns when activated. (Reproduced with permission from [84].)

members of all of the classes referred to above (Figure 4C). For example, the LP neuron has at least 15 different kinds of receptors, including many neuropeptide receptors that converge to activate the same voltage-dependent inward current [118]. Nevertheless, the circuit actions of these peptides are different, because each class of neuron has a different complement of peptide receptors [119].

Modulators coreleased onto the same target may act cooperatively and account for different aspects of the response. In the *Aplysia* feeding system, a cholinergic command-like neuron, CBI-2, coreleases two peptides, FCAP and CP2, onto the same target neurons. Both peptides enhance synaptic transmission, but FCAP increases quantal size, and CP2 increases the quantal content [120]. For many years it has been assumed that neuropeptides are preferentially released by high frequency discharges or bursts, and that single action potentials or low frequency firing would produce little release. However, work on the *Aplysia* neuromuscular system shows that peptide cotransmitters are released over the whole physiological range of activity [121–123]. The quantity of peptide released in response to each spike is dependent on

the mean spike frequency, and different peptides within the same terminals are released in fixed ratios over the whole range of frequencies. In contrast, another study demonstrates that cholinergic and peptidergic vesicles are targeted and mobilized differentially in response to different patterns of stimulation [124]. At other synapses there are indications that a neuron might release a different subset of its cotransmitters from different sets of terminals [109].

Neuromodulators may be released in a paracrine fashion, and act at some distance from their site of release. How spatially confined such release is may determine which components of the CPG are affected. In the stomatogastric nervous system, three descending modulatory neurons contain proctolin [84,85,109,125] (Figure 4D). MCN1 contains proctolin, GABA, and CabTRP1a, MPN contains proctolin and GABA, while MCN7 contains proctolin but not GABA or CabTRP1a. Each of these projection neurons elicits distinct motor patterns from the networks of the STG. This difference is partially, but not completely, attributable to the presence of different complements of cotransmitters in each cell. When CabTRP1a receptors are pharmacologically blocked, the effects of stimulating MCN1 and MPN are still different [126]. How then can the same modulators, released from different neurons, have distinct effects on the CPG? One possibility is that peptidases limit the extent to which neuropeptides diffuse, causing different spatial profiles of peptide concentration. Blocking extracellular peptidases in addition to blocking CabTRP1a receptors resulted in similar network activity when each of the two neuromodulatory neurons was stimulated [127]. Therefore, release from different projection neurons appears to be spatially confined to different regions in the STG neuropil.

The role of intrinsic modulation in CPG operation has been less extensively studied than that of extrinsic neuromodulation. In *Aplysia,* the CPG for biting is modulated by both intrinsic and extrinsic sources. Extrinsic serotonergic modulation from the metacerebral giant cell (MCC) and intrinsic modulation mediated by cerebral peptide-2 (CP-2) released from the CB1-2 interneurons have similar effects on speed and timing of the biting pattern, and the effects of bath application of serotonin and CP-2 occlude each other [128]. However, the neurons providing these neuromodulators are active at different times. MCC activity provides extrinsic modulation predominantly in the preparatory phase for the biting rhythm, while intrinsic peptide release is tied to the activity of the CPG and therefore only occurs during biting. This is an example of sequential use of extrinsic and intrinsic modulation during the execution of a defined behavior.

One of the clearest cases of intrinsic modulation in CPG circuits is found in the *Tritonia* swim circuit in which serotonin released from the dorsal swim interneurons (DSIs) enhances the strength of the synapses made by other neurons in the circuit. Thus, operation of the circuit changes the strength of the synapses within the circuit [87,129,130]. In a recent follow-up study [131], the role of spike timing for the serotonin potentiation was studied. The synapse between one of the ventral swim interneurons (VSI) and the ventral flexion motor neuron (VFN) was enhanced by serotonin, which is released by the DSIs in a manner that depends critically on the relative timing of modulator release and synapse activity [131].

Command Neurons/Modulatory Projection Neurons

In referring to the descending control of CPGs two terms are often used. The first, 'command neuron' dates back about half a century. The second, 'modulatory projection neuron' is more recent and is often used for descending pathways that release neuropeptides and amines. In some cases, it may be useful to distinguish between these two terms, although today they are sometimes used interchangeably. The original 'command neurons' were neurons that were able to activate a complete sequence of movements in response to tonic stimulation [132] (Figure 5A). Subsequently, a 'command neuron,' was rigorously defined as a neuron both necessary and sufficient to elicit a behavior [133]. However, few neurons have been found that satisfy this rigorous definition. CPGs capable of continuous rhythmic activity seem particularly unlikely to have a true command neuron responsible for regulating their activity. Rather, the activity of these CPGs may result from the activity of a network of multiple higher order neurons and modulatory projections.

In principle, the specific firing pattern of an extrinsic neuromodulatory neuron might not be crucial if the modulator acts diffusely and is removed slowly. However, the firing pattern of some modulatory neurons is shaped by synaptic connections from their CPG targets. The proctolinergic MCN1 neuron in the stomatogastric nervous system activates a gastric mill rhythm, and the MCN1 terminal is itself inhibited by one of the neurons of the gastric mill circuit [134]. The period of the gastric mill rhythm is an integer multiple of the faster pyloric period as a consequence of this feedback synapse [135], and the rhythmic pattern of MCN1 activity produced by this feedback synapse results in different gastric and pyloric activity than if the MCN1 is activated tonically [136].

Multifunctional 'Command-Like' Neurons and Overlapping CPG Circuits

The simplest neural circuitry for producing multiple behaviors would be a separate circuit for each behavior, each controlled by a command neuron that activates or suppresses it. However, this arrangement is rarely found in nature. Instead, CPG circuits can be massively reconfigured by modulatory neurons and neuromodulatory substances such that different circuit outputs can be produced by the same circuit elements [137–140]. For example, in the crab STG, MPN uses proctolin to influence the pyloric rhythm and GABA to inhibit other descending neurons from initiating a gastric rhythm [109]. Additionally, different subsets of neurons can be targets of different neuromodulators [119] and this can result in different subsets of neurons activated under different modulatory conditions.

Recent evidence from the *Aplysia* feeding circuitry reveals that it is the concerted activity of multiple

higher-order interneurons that regulates behavioral output in this multifunctional circuit (Figure 5C). *Aplysia* consummatory behavior consists of two forms, ingestion and egestion, each involving the protraction and retraction of the radula. Various combinations of radula movement are evoked by the same pattern generator in response to the concerted activity of the cerebro-buccal interneurons (CBIs) 1, 2, and 3. CBI-2 can most closely be designated a command-like neuron. CBI-2 is excited by food touching the lips [141] and stimulating CBI-2 is sufficient to generate a feeding behavior [142–145]. However, CBI-2 alone is not exclusively responsible for generating relevant consummatory behavior in *Aplysia* [142,143,146]. Rather, it is the combined activities of the command-like CBI-2 in conjunction with the more modulatory CBI-1 and CBI-3 neurons that lead to a behaviorally relevant output [142,143] (Figure 5B,C). For example, CBI-2 stimulation alone produces egestive motor programs, but activation of CBI-3 during CBI-2 elicited rhythms converts egestive rhythms into ingestive rhythms [142]. Thus this pattern-generating circuit is able to generate multiple, behaviorally relevant outputs using the same underlying circuitry selectively activated by higher order interneurons.

Multifunctional neurons also govern the behavior of the leech, *Hirudo medicinalis.* Leeches perform three characteristic motor behaviors: swimming, crawling, and whole-body shortening. The swim circuit is organized hierarchically and contains three levels of interneurons: trigger neurons in the head brain and gating and oscillator interneurons in the individual body segments. Both trigger and gating neurons have command-like features (Figure 5B). When the swim command-like neurons are stimulated, they are capable of inducing swimming behavior [147,148]. However, when external stimuli are applied that elicit shortening behavior, the trigger neurons are excited, but the gating neurons are inhibited [149]. Thus the trigger neurons are multifunctional. In another study, stimulation of the paired R3b1 neurons of the brain elicited either swimming or crawling [150], depending on the depth of bathing solution around the animal. When the bathing solution was deep, swimming was elicited and when it was shallow, crawling was elicited. R3b1 neurons may thus be considered command-like for locomotion generally, but the form of locomotion is selected at lower levels of the circuit hierarchy.

One way in which multiple neurons can interact to determine behavior was found in a recent study in the leech [9]. The authors combined voltage-sensitive dye imaging with electrophysiological stimulation to ask how the leech 'decides' between swimming and crawling in response to a sensory stimulus. The authors imaged approximately half of the neurons in a ganglion simultaneously, and found that a linear combination of the activity of multiple cells was the best predictor of the eventual decision, rather than the activity of any one cell. Stimulating or inhibiting cell 208, a neuron that had a large 'weight' in the linear combination, biased the decision towards swimming or crawling. It seems likely that this system is typical, and that, in general, many

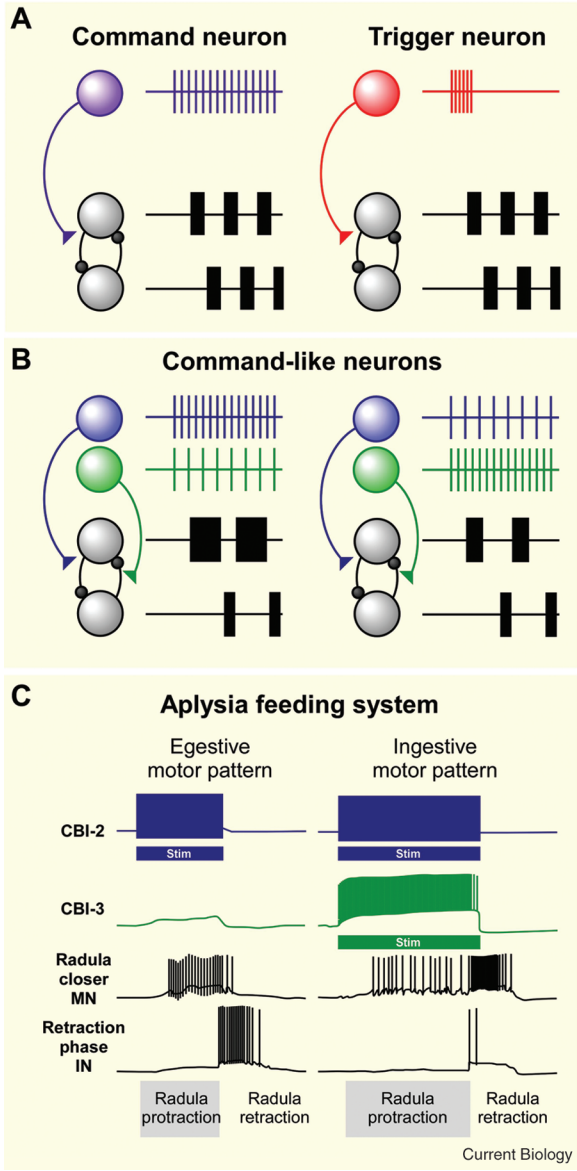

Figure 5. Motor pattern selection.

(A) A command neuron elicits CPG activity that is maintained as long as the command neuron is active. A trigger neuron elicits CPG activity that outlasts the activity of the trigger neuron. (B) Command-like neurons act in concert and may form networks of command-like cells. Differential activity in these neurons produce different CPG output. (C) In the *Aplysia* feeding system, radula protraction and retraction can be coordinated in different ways, resulting in either an ingestive or egestive motor pattern. When two command-like neurons are stimulated differentially, they bias the probability that either of the motor patterns is elicited. Stimulating CBI-2 elicits an egestive-like motor pattern, signified here by high-frequency firing of a radula closer motor neuron during the protraction phase. Simultaneously stimulating CBI-2 and CBI-3 elicits an ingestion-like motor pattern, signified here by high-frequency firing of the same motor neuron during the retraction phase. (Reproduced with permission from [142].)

neurons collectively determine behavioral responses to stimuli.

One neuron can influence multiple unrelated pattern-generator networks. The dorsal swim interneurons in

the mollusk *Tritonia diomedea* are involved in the gating of three different behavioral outputs: swim pattern-generating, reflexive withdrawal [151], and crawling [152]. Swimming and crawling in *Tritonia* are produced by very different locomotory mechanisms — swimming is muscular while crawling is produced by the activation of cilia on the foot, presumably controlled by different circuits.

Although some sensory neurons synapse directly onto CPG neurons [153], sensory neurons may also alter the expression of motor patterns by influencing the activity of modulatory projection neurons. The Ventral Cardiac Neurons (VCNs) are a recently identified set of pressure-sensitive sensory neurons in the crab stomach that synapse onto a number of identified projection neurons [154]. The effects of the VCNs can be accounted for largely on the basis of their activation of MCN1 and CPN2 [155], and sensory activation of different subsets of projection neurons may elicit different forms of STG gastric mill and pyloric rhythms [156].

Although true command neurons are seemingly rare in central pattern generating circuits, there are examples of neurons in these circuits which do appear to fit the classical definition. For example, an apparent command neuron in the CPG for wing stridulation behavior in crickets has been identified [157].

The Role of the Periphery in Producing Motor Output

Movement and behavior are not simple consequences of motor neuron discharge. Invertebrate muscles often show a nonlinear transform between motor neuron activity and contraction, and therefore it is not trivial to predict movement from motor neuron activity [158, 159]. Thus, the periphery plays a role not only in providing sensory feedback but also in post-processing motor commands [160].

Synaptic dynamics at the neuromuscular junction, slow dynamics of the contractile properties of the muscle itself, and neuromodulation of both transmitter release and muscle contractile properties contribute to the nonlinear input–output relation between motor neuron firing and muscle contraction. CPG-driven rhythmic preparations are particularly well-suited to investigate the neuromuscular transform, because of the well-defined temporal structure of motor neuron activity [161]. The relationship between neuron and muscle activity has been studied extensively in muscles moving the radula in the *Aplysia* feeding system and in crustacean stomach muscles innervated by neurons of the STG.

Pyloric stomach muscles in the spiny lobster, *Panulirus interruptus*, like many invertebrate muscles, show graded responses to neuronal input and often do not contract appreciably in response to single presynaptic spikes. Morris and Hooper [162] compared two muscles innervated by the same presynaptic neuron and found that contraction of one predominantly depends on the spike number in the presynaptic burst, while contraction of the other predominantly depends on spike frequency. These muscles relax slowly and show temporal summation between rapid bursts. Consequently, the steady-state contraction in response to regular rhythmic input has a tonic component that is several-fold larger than the phasic contractions resulting from rhythmic input [163]. Presynaptic spike number, spike frequency, cycle period, and burst duty cycle all influence the ratio between phasic and tonic contraction by affecting the rise and relaxation rates differentially [164].

An important consequence of the complex relation between presynaptic burst parameters and phasic and tonic contraction amplitudes is that seemingly small changes in presynaptic activity can have large effects. The pyloric CPG is modulated by other stomatogastric networks with slower rhythmic activity. These interactions manifest as seemingly minor changes in burst parameters of the fast pyloric motor neuron activity. At the level of muscle contractions, however, these small, slow changes are translated into large changes in contraction amplitude, to the point where pyloric muscles predominantly contract in time with slow networks whose neurons do not innervate them [165–167].

In the *Aplysia* feeding system, the muscles that move the radula have been used to study the neuromuscular transform, its role in rhythmic behaviors, and the consequences of its modulation [158,161,168,169]. Here, slow contraction dynamics lead to complex interactions in the way antagonistic closer and opener muscles produce movement. Models of these interactions show that rapid feeding cannot be produced in the absence of mechanisms that change contraction properties, because the muscles cannot relax sufficiently during rapid rhythmic activation [168]. The function of one of the muscles controlling the radula, the accessory radula closer (ARC) muscle, is now relatively well understood [169]. It is innervated by two cholinergic motor neurons which differ in their firing patterns and in their cotransmitters. These modulatory substances have differential effects on relaxation rate and contraction amplitude and are differentially released. This is thought to ensure functional performance over a wide range of different patterns.

When modulators are not released from the motor neurons themselves, it is less obvious how release from extrinsic sources is matched to different types of activity that the motor neurons produce. An example for task-specific activation of modulatory neurons comes from the locust. The octopaminergic efferent dorsal unpaired median (DUM) neurons are a population of segmental modulatory neurons that affect neuromuscular transmission, contraction size and relaxation time, and even metabolic processes in the muscles they innervate. Specific subtypes of these neurons innervate muscles used in specific behaviors, such as walking or flying. It was thought that the DUM neurons functioned as a general arousal system, but recent work shows that during these tasks, DUM neurons are differently centrally activated according to behavioral context [170,171].

Different neuromodulators can affect the temporal dynamics of muscle contraction differently [172]. Although some crustacean stomach muscles are

innervated by inhibitory and modulatory terminals in addition to their excitatory motor terminal innervation [173], many circulating neurohormones reach the STG, neuromuscular nerve terminals and muscles. It is not known if central and peripheral targeting of the same substances are coordinated in the stomatogastric system, but this question has recently been addressed in the cardiac ganglion, which drives the heart [174]. Here, a single extrinsic modulatory neuron releases dopamine both close to the heart muscle, and directly into the neuropil of the cardiac ganglion. Dopamine directly increases contraction amplitude of the heart and increases burst frequency by acting on cardiac ganglion interneurons. Interestingly, both effects counteract a dopamine-induced increase in burst duration and number of spikes in the cardiac motor neurons. Therefore, feedback mechanisms present in the intact integrated central pattern generator-effector system reveal a different effect of dopamine on movement production than can be inferred from the actions it has on the isolated cardiac ganglion [174].

Development and Homeostasis

The past few years have seen a tremendous amount of new work on the development of CPGs in vertebrates [5,175] as molecular methods, genetic manipulations, and the development of new *in vitro* preparations offer the promise that identification of CPG neurons in the vertebrate spinal cord and brainstem will be possible. At the same time, progress on the development of CPGs in invertebrates has been modest, as we know relatively little about the adult CPGs of the invertebrate preparations best suited for developmental studies: the fruitfly *Drosophila* and the nematode *Caenorhabditis elegans*. Nonetheless, in a landmark paper Suster and Bate [3] genetically removed most of the sensory neurons in *Drosophila*, and found that the CPG for embryonic and larval locomotion developed without most of the sensory neurons providing feedback for locomotion.

Despite the fact that developmental studies of the 'classic' CPGs such as those in *Aplysia*, leech and the STG have been hindered by the lack of genetic tools and/or long generation times, some interesting findings are becoming available. A recent study [176] describes the sequential development of electrical and chemical connections in the circuit that governs local bending in the leech embryo. Early in embryonic development, touching the body wall elicits contraction around the entire perimeter, largely due to electrical synapses that are formed early. Later in development, the same touch evokes an adult-like local bending behavior, accompanied by the development of chemical inhibitory synapses.

The motor patterns produced by the stomatogastric nervous system change during development. In the adult STG, the neurons are roughly divided into two circuits, those that produce the pyloric rhythm and those that produce the gastric mill rhythm, although neurons can switch back and forth between these networks [140,177]. In contrast, in the embryo and early larval stages, all of the neurons in the STG are active in a single embryonic rhythm [178,179] that is often irregular [180,181]. However, when the descending modulatory inputs are removed in the embryo, and oxotremorine applied, the embryonic STG produces pyloric-like and gastric mill-like rhythms [179], suggesting that the backbone of the adult circuit is already present early in development, but that the embryonic neuromodulatory environment could be responsible for the configuration of the circuit that produces the embryonic rhythm. The modulatory inputs to the STG acquire their modulatory substances sequentially over embryonic and larval time [182–184] although many of the hormonal inputs to the STG are present early in development [107], and the embryonic STG appears to respond to all of the neuromodulators that act on the adult [181,184,185]. There is not yet a clear explanation for the differences between the embryonic and adult rhythms, although the suggestion has been made that enhanced electrical coupling could be responsible [186].

In animals that live for a long time the CPGs that control locomotion, heartbeat, respiration, and feeding must function adequately for many years. For example, lobsters only reach the minimal commercial size after 5–7 years, and, in the absence of human predation, easily live for 25 years. The existence of mechanisms that maintain stable CPG function despite major perturbations is illustrated in a series of experiments in which neuromodulatory inputs to the adult STG are removed, resulting in loss of rhythmic activity. However, over 1–5 days, rhythmic activity returns [46,187–190], now independent of neuromodulator action. This argues that neurons in the CPG respond to either the loss of their own activity, or the loss of neuromodulator, by altering their own excitability properties to ensure proper circuit function.

Conclusions

What overarching generalizations can we offer workers on vertebrate preparations as they attempt to unravel the mechanisms of circuit function? First, trying to understand how a circuit works without being able to identify the component neurons is impossible. Unambiguous determination of connectivity among the component neurons is required. Nonetheless, even a detailed connectivity diagram among identified neurons is only a starting point to understanding the dynamics of circuit operation. Neuromodulation of intrinsic and synaptic properties together with history-dependent processes such as depression, facilitation and inactivation play a role in shaping how networks perform. Second, neuromodulation is widespread and many neuromodulatory neurons act in concert to configure circuits into multiple possible output patterns. Third, to the extent to which a circuit is important for the animal's success in the world, it is likely that similar circuit outputs may be achieved by multiple, overlapping mechanisms. It is tempting to argue that the small number of neurons in invertebrate networks requires mechanisms to produce flexible outputs that large circuits do not use. It seems far more likely, however, that all

of the mechanisms that allow invertebrate CPGs to be both stable and flexible are used in the vertebrate nervous system to provide skilled motor performance and other higher cognitive functions.

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