Understanding Circuit Dynamics Using the Stomatogastric Nervous System of Lobsters and Crabs

Eve Marder[1] and Dirk Bucher[2]

[1]Volen Center and Biology Department, Brandeis University, Waltham, Massachusetts 02454; email: marder@brandeis.edu

[2]The Whitney Laboratory for Marine Bioscience, University of Florida, St. Augustine, Florida 32080; email: bucher@whitney.ufl.edu

Annu. Rev. Physiol. 2007. 69:291–316

First published online as a Review in Advance on September 29, 2006

The *Annual Review of Physiology* is online at http://physiol.annualreviews.org

This article's doi: 10.1146/annurev.physiol.69.031905.161516

0066-4278/07/0315-0291$20.00

Key Words

central pattern generator, neuronal oscillators, neuromodulation, pyloric rhythm, gastric mill rhythm

Abstract

Studies of the stomatogastric nervous systems of lobsters and crabs have led to numerous insights into the cellular and circuit mechanisms that generate rhythmic motor patterns. The small number of easily identifiable neurons allowed the establishment of connectivity diagrams among the neurons of the stomatogastric ganglion. We now know that (*a*) neuromodulatory substances reconfigure circuit dynamics by altering synaptic strength and voltage-dependent conductances and (*b*) individual neurons can switch among different functional circuits. Computational and experimental studies of single-neuron and network homeostatic regulation have provided insight into compensatory mechanisms that can underlie stable network performance. Many of the observations first made using the stomatogastric nervous system can be generalized to other invertebrate and vertebrate circuits.

INTRODUCTION

STNS: stomatogastric nervous system

STG: stomatogastric ganglion

Recent years have seen a rebirth of interest in understanding how neural circuits generate behavior. Therefore, it is a particularly good time to review and critically examine what we know about the stomatogastric nervous system (STNS), one of the premier systems for analyzing how circuit dynamics arise from the properties of its neurons and their connections. The process of understanding how the STNS generates movements of the crustacean foregut has involved multiple cycles of revisiting many of the same issues over the years, as each decade has revealed "new generation" insights into how even this small nervous system generates rhythmic motor patterns.

The STNS was developed as an experimental preparation almost 40 years ago, in the early days of circuit analysis (1), to understand the generation of rhythmic motor patterns. Over time this system has revealed numerous general principles relevant to central pattern generators (CPGs) and other large and small circuits in both invertebrates and vertebrates. As we look forward to understanding the larger and more complex circuits in the vertebrate brain, lessons learned in small circuits can help pose more precisely the issues crucial for circuit analysis in all systems.

The 40 years of work on the STNS have generated a considerable literature now nearing almost 1000 original journal articles, many reviews (e.g., References 2–4), and two books (5, 6). Navigating through this literature can be a daunting task, made more difficult because studies of the STNS have employed a number of different crustacean species, including spiny lobsters (*Panulirus argus*, *Panulirus interruptus*), clawed lobsters (*Homarus americanus* and *Homarus gammarus*), a variety of crabs (*Cancer borealis* most commonly), crayfish, and shrimp. Although all big-picture conclusions that have arisen from STNS studies hold for all species, some details do vary across species (7).

Features of the Stomatogastric Nervous System that Facilitate Circuit Analysis

The STNS has important attributes that have been crucial in making it a useful preparation for circuit analysis:

1. When the STNS is removed from the animal and placed in a saline-filled dish, it continues to produce fictive motor patterns that resemble closely those recorded in vivo (8–12).
2. The neurons of the stomatogastric ganglion (STG) are unambiguously identifiable from preparation to preparation.
3. Intracellular recordings from the somata of the STG neurons reveal large-amplitude synaptic potentials and other underlying subthreshold changes in membrane potential.
4. Unlike most CPGs that consist of interneurons that drive motor neurons (13), most of the synaptic connections important for the generation of rhythmic motor patterns in the STG occur among the motor neurons. Thus, recordings from the motor neurons provide, at the same time, recordings of the output as well as of the operation of the circuit.
5. It is routinely possible to obtain simultaneous recordings of most, if not all, relevant circuit neurons, using a combination of intracellular and extracellular recordings. Routine STNS experiments include 4 simultaneous intracellular recordings and 8–12 extracellular nerve recordings.
6. The large neuronal somata allow hand dissection of individual neurons for biochemical and molecular characterization at the single-neuron level (14–16).
7. The in vitro preparations are routinely stably active for 18–24 h and can be maintained for days and weeks if required (17).

Today, as we look at attempts to understand vertebrate spinal cord, brainstem, and

brain circuits, work is hampered because of the lack of one or more of the above attributes. For this reason, attempts to identify neurons unambiguously in vertebrates are critical (18, 19).

ORGANIZATION OF THE CRUSTACEAN STOMATOGASTRIC NERVOUS SYSTEM

The STNS controls the movements of four regions of the crustacean foregut, or stomach. **Figure 1*a*** shows a side view of a lobster and indicates the position of the stomach, the heart, and the main portions of the nervous system. The STG is found in the dorsal artery, where it is a direct target for hormones released from the pericardial organs and other sources. The crustacean stomach (**Figure 1*b***) is a complex mechanical device that grinds and filters food, using the movements made by more than 40 pairs of striated muscles (20). The stomach muscles, which move the gastric mill and pylorus, are innervated by motor neurons in the STG. Although the general features of the stomach are conserved across decapods, the shape of the stomach is quite different in the oblong lobster and the flat crab. These animals also show anatomical differences in the nervous system and in the STG.

The STNS consists of a group of four linked ganglia, the paired commissural ganglia (CoGs), the unpaired esophageal ganglion (OG), and the STG (**Figure 1*b*,*c***). Each of the CoGs contains approximately 400 neurons, and the OG contains approximately 18 neurons. Together the CoGs and OG contain many descending modulatory neurons that control STG activity (21, 22). The STG consists of ~30 neurons [the exact number varies from species to species and, for some cell types, from animal to animal within a species (23, 24)] and contains the motor neurons that move the muscles of the gastric mill and pyloric regions of the stomach (**Figure 1*b***) (20).

Figure 1*c* is a diagram of the STNS dissected free from the stomach as it is routinely prepared for in vitro electrophysiological recordings. Intracellular glass microelectrodes are used to record from the somata of STG neurons, and extracellular nerve recordings are used to identify STG neurons and to characterize motor patterns. In **Figure 1*d***, simultaneous extracellular recordings of all the motor neurons show the pyloric and gastric mill rhythms in the lobster *H. americanus*. As we discuss below, the pyloric rhythm is faster than the gastric mill rhythm, and although they can usually be separately characterized, there are also strong interactions between them.

In addition to the gastric mill and pyloric rhythms, the STNS also generates the cardiac sac and esophageal rhythms. The generation of these latter two rhythms depends on neurons not found in the STG, and the circuits responsible for them are not known.

CoG: commissural ganglion

OG: esophageal ganglion

GM neuron: gastric mill neuron

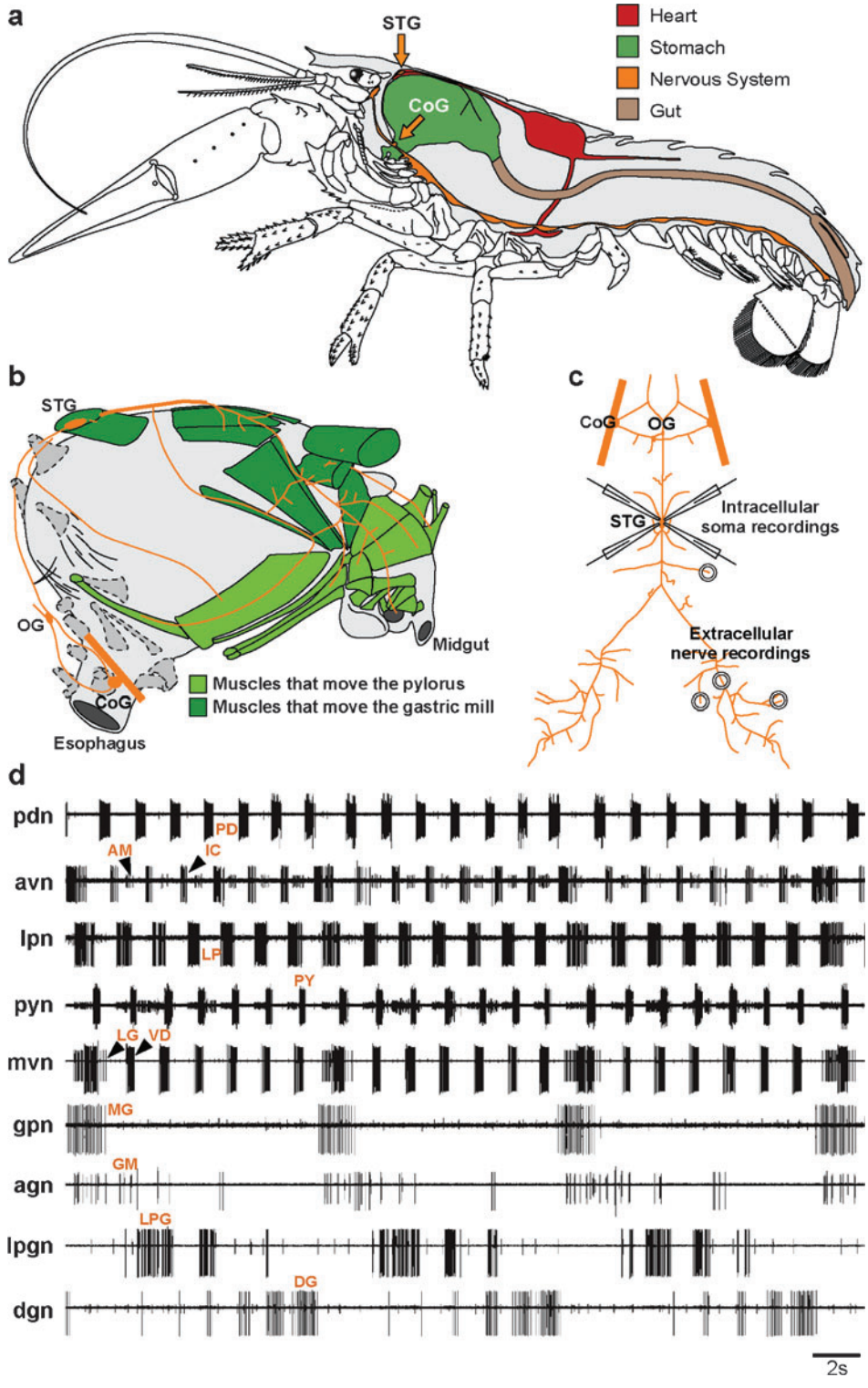
PY neuron: pyloric neuron

PD neuron: pyloric dilator neuron

THE STRUCTURE OF THE SOMATOGASTRIC GANGLION AND ITS NEURONS

The number of STG neurons varies from 25–26 in the crab *C. borealis* (23), 28–30 in *P. interruptus* (20), and 29–32 in *H. americanus* (24). Differences in the number of two of the neuron types in the STG, the gastric mill (GM) and pyloric (PY) neurons, account for much of this variability, whereas all other neurons are found invariantly as either single copies or pairs of neurons (24).

STG neurons have a large soma (typically 50–100 μm) and complex branching patterns. **Figure 2** shows dye fills of a single pyloric dilator (PD) neuron in the three species indicated. These fills illustrate both the structures of the individual neurons and the differences in ganglion shape and size of the adult animals routinely used for physiological analyses. Many STG neurons have major neurites as large as 15–20 μm in diameter, with fine diameter processes that ramify extensively through much of the neuropil. Synaptic profiles are found on these finer processes (23–26).



THE STOMATOGASTRIC GANGLION IS MULTIPLY MODULATED

Many studies have identified the neurotransmitters used by the STG neurons themselves (14, 27, 28) and the neuromodulators that are released into the neuropil of the STG as a consequence of the actions of sensory neurons and descending modulatory projection neurons (22, 29–31). Additionally, researchers have characterized the substances found in the pericardial organs and other neurosecretory structures (32, 33). Thirty years ago, these studies employed biochemical and histochemical methods (34, 35). Subsequently, enormous progress was made with immunocytochemical methods (36–38). Most recently, the introduction of mass spectroscopy for peptide identification has accelerated the pace of neuropeptide identification in the crustacean nervous system (39, 40).

Figure 3 summarizes much of what is known about the neuromodulatory control pathways to the STG. An important take-home message for workers in other circuits is that the STG is multiply modulated. Consequently, no single substance or several substances are the major source of neuromodulatory inputs to the STG. Rather, the challenge is to understand which of these substances are colocalized in specific neurons (31, 41), to understand the extent to which these substances act at the same time or different times to regulate the networks of the STG, and to uncover the mechanisms by which each of these substances regulates STG motor patterns.

Many of the same substances are released into the hemolymph to act as circulating hormones and are released directly into the STG neuropil from descending modulatory projections (**Figure 3**). Presumably, many of the circulating hormones are released in the context of specific behavioral states such as feeding (42) or molting (43). However, a detailed understanding of how neuromodulatory hemolymph concentrations fluctuate according to the animal's behavioral state (44) is still lacking for most of the substances listed in **Figure 3** (left panel).

THE PYLORIC RHYTHM

Electromyographic recordings made in vivo show that the pyloric rhythm is almost always continuously expressed in the intact animal, although its frequency and intensity vary with the animal's physiological status (8, 9). The pyloric rhythm recorded in vitro closely

Figure 1

The stomatogastric nervous system (STNS). (*a*) Side view of a lobster showing the position of the stomach and the STNS. CoG, commissural ganglion; STG, stomatogastric ganglion. (*b*) Side view of the lobster stomach showing the muscles that move the pylorus and gastric mill, the ganglia of the STNS, and the location of the major motor nerves innervating the stomach muscles. OG, esophageal ganglion. (*c*) Schematic of the STNS as it is usually studied in vitro. The nerves and ganglia are dissected off free of the stomach. Extracellular recordings are made with pin electrodes placed in Vaseline wells around the motor nerves. Intracellular recordings are made with glass microelectrodes from ganglia somata. (*d*) Simultaneous extracellular recordings from nine different nerves (pdn, avn, lpn, pyn, mvn gpn, agn, lpgn, and dgn, where the "n" refers to "nerve"). Recordings show the activity of each of the STG motor neurons during ongoing gastric mill and pyloric rhythms in the lobster *H. americanus*. The pyloric rhythm is the faster rhythm and is seen as the alternating activity of the pyloric dilator (PD), lateral pyloric (LP), pyloric (PY), ventricular dilator (VD), and inferior cardiac (IC) neurons. The gastric mill rhythm is slower and is seen as the bursts of activity in the medial gastric (MG), dorsal gastric (DG), gastric mill (GM), lateral posterior gastric (LPG), and lateral gastric (LG) neurons. The DG and LPG neuron bursts are interrupted in time with the pyloric rhythm. agn, anterior gastric nerve; AM, anterior median neuron, avn, anterior ventricular nerve; IC, inferior cardiac neuron; mvn, median ventricular neuron; gpn, gastropyloric nerve. *a* is modified from Reference 189, and *b–d* are modified, with permission, from Reference 140.

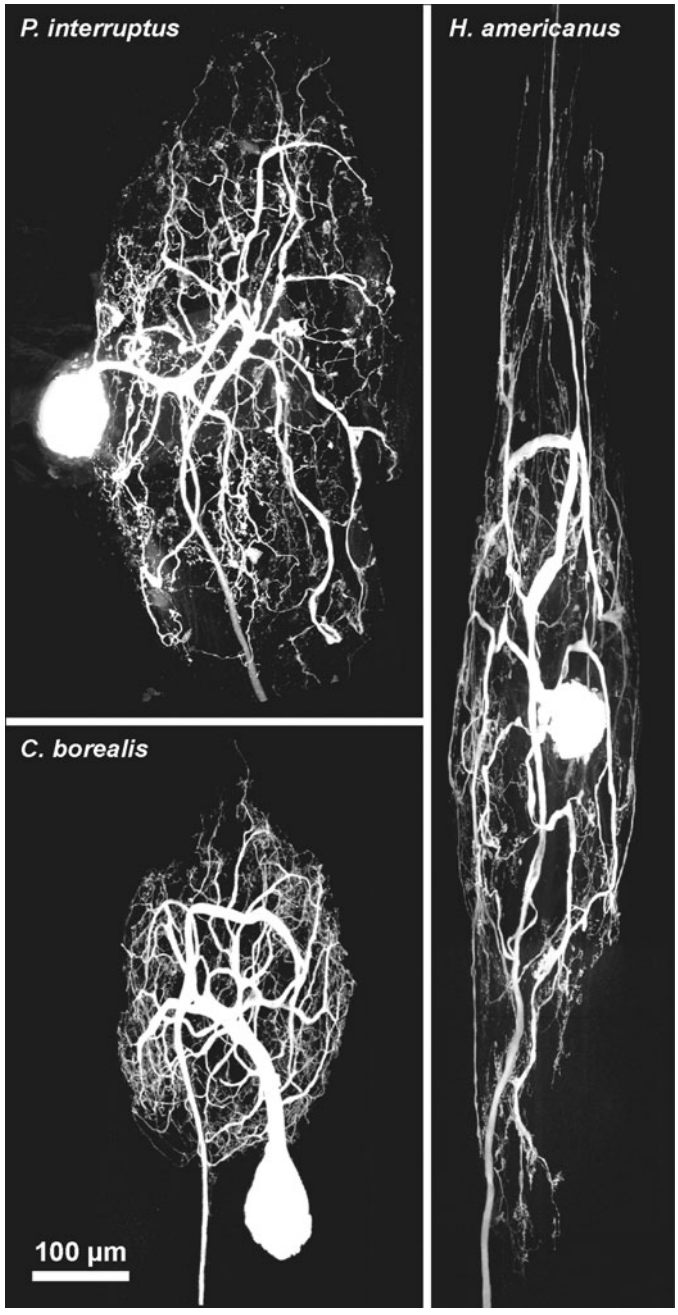


Figure 2

Structure of the pyloric dilator neurons in three crustacean species. In each case, the neurons were filled with Alexa 568 hydrazide and imaged with a confocal microscope. Scale bar is the same for all three images. *H. americanus* fill is used, with permission, from Reference 140, *P. interruptus* fill is courtesy of J. Thuma & S.L. Hooper (unpublished work), and *C. borealis* fill is from D. Bucher (unpublished work).

resembles those recorded in vivo (30). The pyloric rhythm is a triphasic motor pattern with a period of ~1–2 s (**Figure 4**). The canonical pyloric rhythm consists of bursts of action potentials in the PD neurons, followed by bursts of action potentials in the lateral pyloric (LP) neuron, then by bursts in the PY neurons. The inferior cardiac (IC) neuron fires often with the LP neuron burst, and the ventricular dilator (VD) neuron commonly fires with the PY neurons. The anterior burster (AB) neuron is an interneuron that projects anteriorly through the stomatogastric nerve to the CoGs and is electrically coupled to the PD neurons.

Early research on the pyloric rhythm (1, 45–49) focused on several fundamental questions. (*a*) What is the underlying mechanism for rhythm production? (*b*) What determines the specific phase relationships or timing of the elements within the pattern? (*c*) What determines the frequency of the rhythm? Researchers are asking these same questions today of vertebrate spinal cord and respiratory circuits (50–53).

The first steps in answering those questions were to determine the intrinsic membrane properties of each of the pyloric network neurons and to determine their connectivity. There are two major classes of inputs to the pyloric network neurons: inputs from other neurons within the pyloric network itself and inputs from the anterior CoGs and OG. Therefore, the intrinsic properties of the pyloric neurons have been studied under two conditions: (*a*) with impulse activity from the anterior inputs blocked or removed and STG presynaptic inputs also blocked and (*b*) with anterior inputs left intact but STG level presynaptic inputs removed. To remove synaptic inputs from other STG neurons, researchers (*a*) block the glutamatergic inhibitory synaptic inputs with 10^{-5} M picrotoxin (27, 54, 55) and (*b*) remove other inputs, including electrically coupled neurons, by photoinactivation after injection with a fluorescent dye such as Lucifer yellow (56). In the presence of the descending modulatory inputs, all STG neurons show some evidence

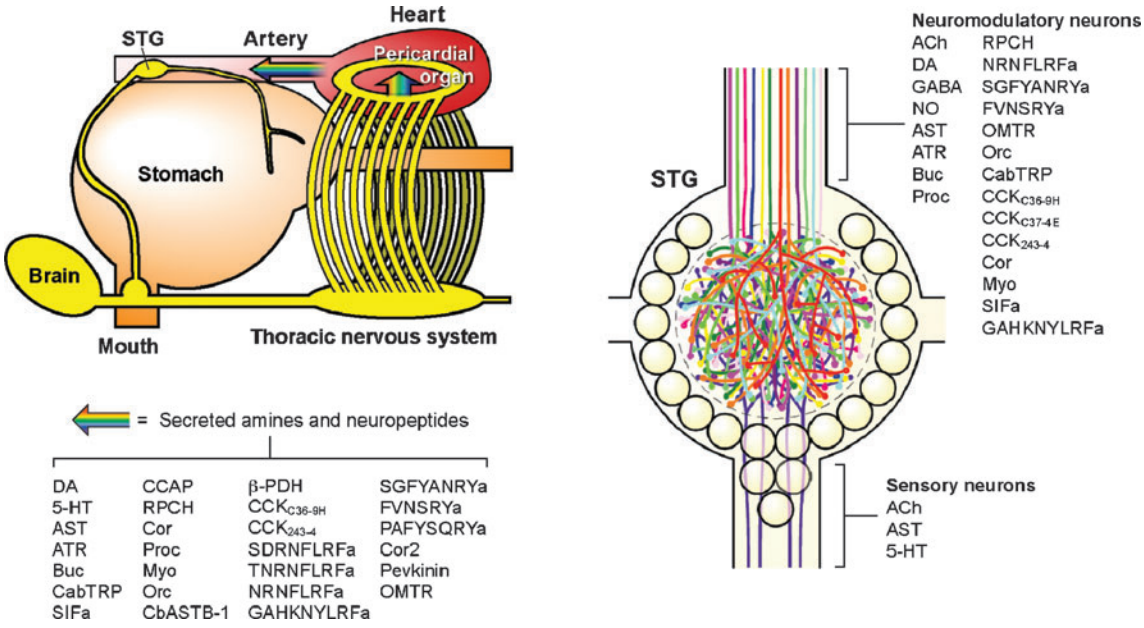


Figure 3

Neuromodulatory control of the stomatogastric ganglion (STG). (*Left*) The STG is shown in the dorsal artery, directly anterior to the heart. The pericardial organs are neurosecretory structures that release many amines and neuropeptides directly into the circulatory system at the level of the heart. (*Right*) The STG is directly modulated by terminals of descending neuromodulatory neurons and ascending sensory neurons. These direct neural projections also release many small molecules and neuropeptides into the neuropil of the STG. Modified from Reference 190.

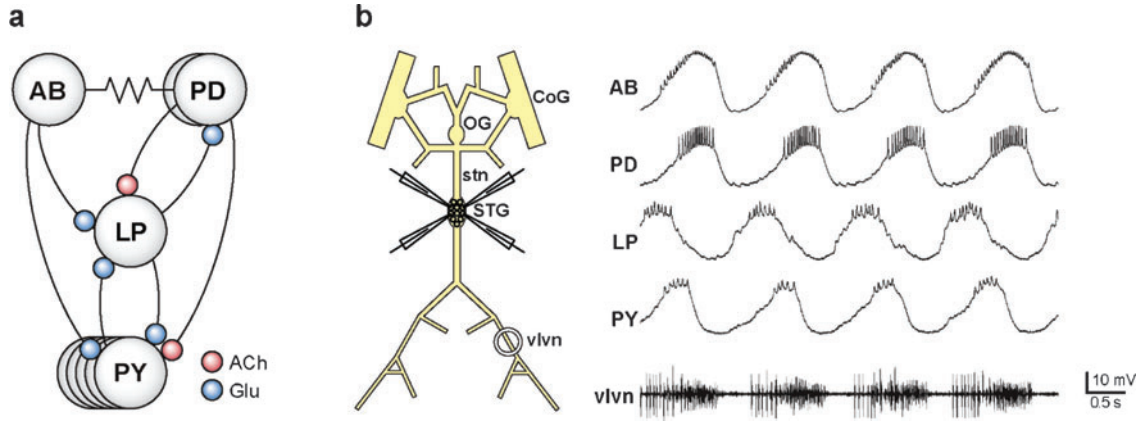


Figure 4

The pyloric rhythm. (*a*) Simplified connectivity diagram of the pyloric circuit [without the ventricular dilator (VD) and inferior cardiac (IC) neurons]. A resistor symbol indicates an electrical coupling between an anterior burster (AB) neuron and a pyloric dilator (PD) neuron. Circles indicate chemical inhibitory connections (ACh, cholinergic; Glu, glutamatergic). (*b*) Schematic of the stomatogastric nervous system (STNS) and simultaneous intracellular (*top four traces*) and extracellular (*bottom trace*) recordings from *H. americanus* that show the typical triphasic pattern. CoG, commissural ganglion; OG, esophageal ganglion; stn, stomatogastric nerve; vlvn, ventral branch, lateral ventricular nerve.

LP neuron: lateral pyloric neuron

IC neuron: inferior cardiac neuron

VD neuron: ventricular dilator neuron

AB neuron: anterior burster neuron

of plateau or bursting behavior (49, 57, 58). However, after the descending inputs are removed, only the AB neuron retains its ability to burst (48, 59), whereas the other neurons fire tonically or fall silent.

Investigators determined the connectivity among the pyloric network neurons, using a combination of simultaneous intracellular recordings and cell kills (1, 47, 55). **Figure 4*a*** shows (*a*) a simplified connectivity diagram of the pyloric network neurons that supports the generation of the pyloric rhythm and (*b*) the neurotransmitters that mediate these synaptic connections. **Figure 4*b*** shows simultaneous intracellular recordings from the somata of these neurons in *H. americanus*.

A first-approximation description of the pyloric rhythm is as follows. The AB neuron is an intrinsic oscillator that, by virtue of its electrical coupling with the PD neurons, causes them to fire bursts of action potentials. Together the PD and AB neurons inhibit the LP and PY neurons, forcing them to fire in alternation with the PD neurons. The LP neuron rebounds from inhibition before the PY neurons, because of various factors, and in turn inhibits the PY neurons. When the PY neurons finally rebound from inhibition, they terminate the LP neuron burst. In this scenario, the rhythm depends strongly on the intrinsic pacemaker properties of the AB neuron, and the phase of the pattern depends on a variety of factors that govern the time at which the LP and PY neurons rebound from inhibition (45, 60–62).

Neuromodulation of the Stomatogastric Ganglion Circuits

Many different substances, including amines, neuropeptides, and gases, modulate the pyloric circuit directly (**Figure 2**) (36, 38, 63–74). Exogenous application of these substances results in changes in the frequency, phase relationships, and number of spikes per burst in different network neurons so that the same network can be reconfigured into various different output patterns (22, 75, 76). Intensive study over the past 20 years has provided some important insights into the mechanisms by which neuromodulatory control is effected in the STG:

(a) Some neuromodulators act on several different voltage-gated channels in the same neuron (77, 78) (**Figure 5*a***).

(b) A number of different neuromodulators converge onto the same voltage-dependent conductance (74) (**Figure 5*b***).

(c) Every neuron in the pyloric circuit is subject to neuromodulation by multiple substances (65, 74, 79).

(d) Every synapse in the pyloric circuit is subject to neuromodulation (78, 80).

(e) The same modulator can influence different synapses in opposing directions (80).

Figure 5*a* summarizes the multiple actions of dopamine on the pyloric neurons in *P. interruptus* (60, 78, 81–83). All pyloric neurons have dopamine receptors, and in each cell type dopamine modulates a different subset of ion channels. Dopamine action on the same channel type can have a different sign in different neurons. Dopamine also modulates the majority of synapses in the pyloric circuits (not shown in **Figure 5*a***).

All STG neurons have receptors for multiple transmitters and neuromodulators. **Figure 5*b*** depicts the known complement of receptors in the *C. borealis* LP neuron. These include receptors to classical transmitters, amines, and a range of neuropeptides. The neuropeptide proctolin was the first to be described to activate a voltage-gated cation current in STG neurons (84), now referred to as the proctolin current. However, later work showed that many of the excitatory neuropeptide receptors found in a given pyloric neuron converge onto the same current (73, 74). Thus, differential circuit modulation by different peptides is the result of different complements of receptors in different neurons. Together, these findings demonstrate that all components of the circuit are subject to neuromodulatory control. This raises a number of

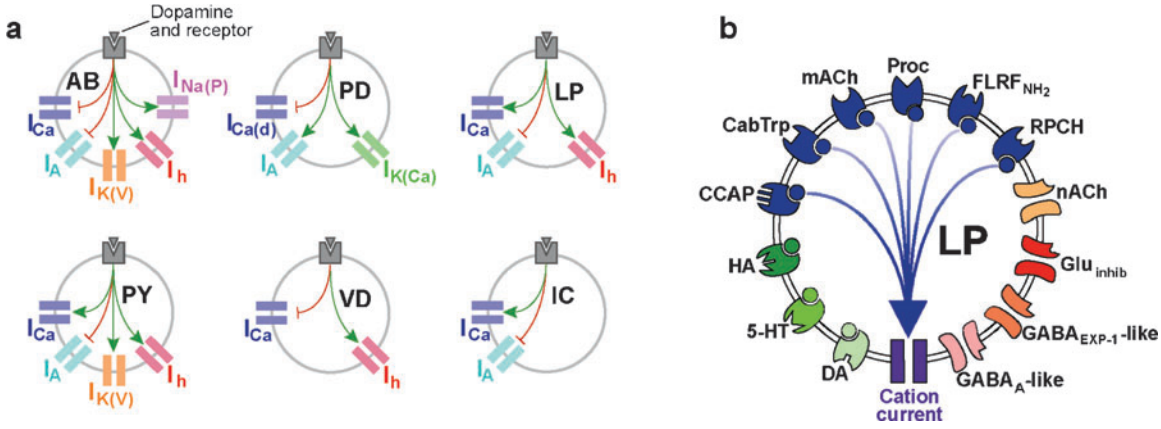


Figure 5

Multiple neuromodulatory mechanisms. (*a*) Dopamine receptors are on all pyloric neurons in *P. interruptus*. In each cell type, dopamine modulates a different subset of ion channels. Dopamine action on the same channel type can have a different sign in different neurons. These schematics summarize data contained in numerous publications from the Harris-Warrick laboratory (60, 78, 81–83). AB, anterior burster neuron; IC, inferior cardiac neuron; LP, lateral pyloric neuron; PD, pyloric dilator neuron; PY, pyloric neuron; VD, ventricular dilator neuron. (*b*) The LP neuron in *C. borealis* has receptors for more than 10 neurotransmitters and modulators, many of which converge on the same cation current. Summarizes data from References 73 and 74 and unpublished data.

questions relevant to maintaining stable circuit function, as it is difficult to understand how it is possible to alter every parameter controlling network function while retaining many of the essential features of the circuit performance.

The Descending Modulatory Projection Neurons

The existence of descending pathways that could influence STG motor patterns was established early (85–87) in spiny lobsters. The anterior pyloric modulator (APM) neuron was an early example of a modulatory neuron that changed the excitability and plateau properties of its target neurons as well as altered the phase relationships of the STG motor patterns (88, 89). Subsequently, the most extensive studies of modulatory projection neurons and their interactions with STG target circuits have been done in *C. borealis*, which has approximately 25 pairs of descending projection neurons to the STG (21).

Some of the descending projection neurons receive synaptic connections from their target neurons in the STG, creating a local circuit among these terminals and STG neurons (90, 91). Consequently, tonic projection neuron activity can be locally configured into rhythmic transmitter release by presynaptic actions.

Most, if not all, of the descending modulatory neurons contain multiple cotransmitters (31, 41, 92), which can evoke a variety of postsynaptic actions and act on different target neurons (93, 94). Sensory inputs can activate these modulatory projection neurons (95–99) to evoke specific sets of motor patterns from the STG circuits.

Maintenance of Constant Phase While Frequency Varies Depends on Synaptic Depression and I_A

One of the remarkable features of the pyloric rhythm is that the phase at which the follower neurons fire is relatively constant while the frequency varies (61, 100–105). This is at first glance puzzling, as all membrane and synaptic currents that play a role

in determining rebound properties have fixed time constants. Nonetheless, recent work has provided some insight into how this may occur. The synapses among STG neurons have both spike-mediated and graded components (106, 107), and the graded component of many of the synapses depresses (108, 109) such that the synaptic current decreases at higher frequencies and increases at lower burst frequencies. The transient outward current I_A and the hyperpolarization-activated inward current I_h play important roles in determining when a follower neuron recovers from inhibition (3, 60, 83, 110). Because I_A requires hyperpolarization to remove inactivation, a short interburst interval decreases I_A. Thus, the effects of frequency on synaptic depression and on I_A interact to promote phase constancy (104).

Frequency Control in a Pacemaker-Driven Network

How is frequency controlled in pacemaker-driven networks? To a first approximation, the AB neuron is the pacemaker for the pyloric network. However, it is electrically coupled to the two PD neurons, and the PD neurons are inhibited by the LP neuron. To what extent do these interactions influence the frequency of the pyloric rhythm?

The AB neuron and the PD neurons burst synchronously, but they release different neurotransmitters (27), respond to different neuromodulators (59), and have different intrinsic membrane properties (49). Under some neuromodulatory conditions, the frequency of the entire pacemaker kernel is significantly slower than that of the isolated AB neuron (65). Motivated by this result, Kepler et al. (111) constructed simple, two-neuron, electrically coupled circuits in which one neuron was an oscillator and the second neuron, nonoscillatory. This study demonstrated that, depending on the nature of the oscillator, a nonoscillatory neuron could either increase or decrease the frequency of the oscillator to which it was electrically coupled. A recent modeling study (112) of the electrically coupled PD and AB neurons suggests that the coupling between two dissimilar neurons may extend the range of frequencies over which the coupled network is stable.

The only feedback to the electrically coupled pacemaker kernel from the rest of the pyloric circuit comes from a synapse from the LP neuron to the PD neurons. The role of this synapse in controlling the frequency of the pyloric rhythm has been somewhat elusive. Hyperpolarizing the LP neuron, or otherwise removing it, sometimes had little effect and other times increased the frequency of the pyloric rhythm (113). This is explained by the phase-response curve of the PD neurons (114–117), which is flat at the phase of the pyloric cycle during which the LP neuron usually fires. Because of this, neuromodulators that strongly potentiate the strength of this synapse can nonetheless have relatively little effect on the frequency of the pyloric rhythm (117).

Many modulators influence the frequency of the pyloric rhythm (59, 65–67, 79, 118), and many of these act directly on the AB neuron (59, 65, 79, 118). Although there are few voltage clamp data available on the isolated AB neuron, Harris-Warrick & Flamm (119) showed that whereas the slow wave that sustains bursting persists in the presence of TTX in dopamine, all slow-wave activity is lost in TTX in octopamine and serotonin. This suggests that a different balance of voltage-dependent currents underlies bursting in different modulators. This intuition is strengthened by modeling studies (120–123) that show that various combinations of conductance densities can sustain similar-looking bursting activity.

THE GASTRIC MILL RHYTHM

The gastric mill rhythm controls the movements of the two lateral teeth and single medial tooth in the inside of the stomach (**Figure 6*a***). Unlike the pyloric rhythm, which in vivo is continuously expressed, the

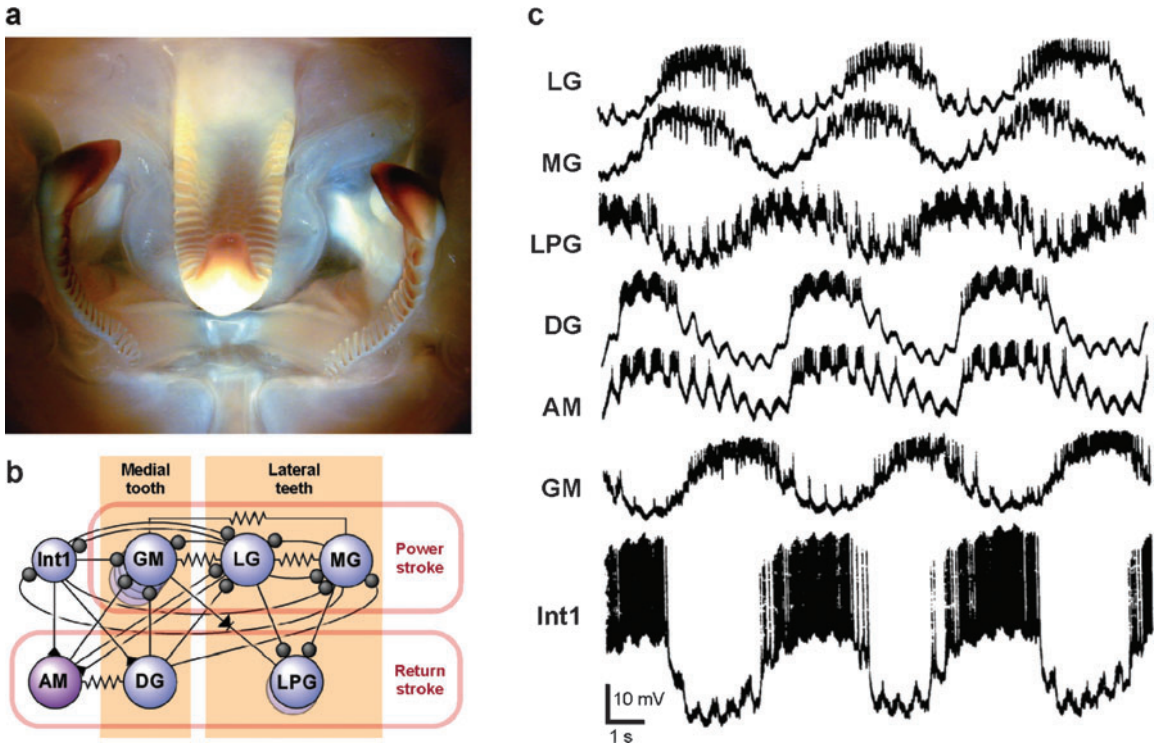


Figure 6

The gastric mill rhythm. (*a*) Photograph of the gastric mill teeth inside the stomach of *P. interruptus*. (*b*) Diagram of the gastric mill circuit. Circles indicate inhibitory connections, triangles indicate excitatory connections, resistor symbols indicate electrical coupling, and the diode symbol indicates a rectifying electrical synapse. Neurons are grouped according to which teeth they control and in which phase they are active. The anterior median (AM) neuron is shown in a different color because it innervates a cardiac sac muscle. Modified with permission from Reference 191. DG, dorsal gastric neuron; GM, gastric mill neuron; Int1, interneuron 1; LG, lateral gastric neuron; LPG, lateral posterior gastric neuron; MG, medial gastric neuron. (*c*) Intracellular recordings of gastric mill neurons in *P. interruptus*. Alternating activity is seen between the LG, MG, and GM neurons in one phase and the LPG, DG, AM, and Int1 neurons in the other phase. The membrane potentials show substantial modulation in pyloric time. Modified with permission from Reference 12.

gastric rhythm in vivo is intermittently active (8) in response to feeding (124, 125) and has a highly variable period, most often approximately 8–20 s. The gastric mill rhythm is less stereotyped than the pyloric rhythm: It displays a number of different forms, depending on how it is activated, that are characterized by different phase relations among the participating muscles and the neurons that innervate them (8, 11, 99, 126, 127). Unlike the pyloric rhythm, the gastric mill rhythm does not have a single pacemaker neuron within the STG, but as a first approximation, the gastric mill rhythm is an emergent property of the reciprocal inhibition among the participating network neurons (128, 129) and interactions with ascending and descending projection neurons (90, 99, 126, 127, 130).

Mulloney & Selverston (128, 129, 131) generated the first connectivity diagram for the gastric rhythm (**Figure 6*b***), using the lobster *P. interruptus*. Heinzel (10, 11) and Heinzel & Selverston (12) further characterized extensively the *P. interrruptus* gastric mill rhythms, using a combination of endoscopy and physiology. **Figure 6*c*** shows

DG neuron: dorsal gastric neuron

LG neuron: lateral gastric neuron

MG neuron: medial gastric neuron

LPG neuron: lateral posterior gastric neuron

simultaneous intracellular recordings from all neurons that participate in the gastric mill rhythm in *P. interruptus*. Note the alternation between dorsal gastric (DG) neurons and GM neurons, which control the medial tooth movements, and the alternation between the lateral gastric (LG) neuron/medial gastric (MG) neurons and the lateral posterior gastric (LPG) neurons, which control the movements of the lateral teeth.

Subsequently, a great deal of work has been done on the gastric mill rhythms activated by specific modulatory projection neurons in the crab *C. borealis* (41, 90, 98, 132, 133). **Figure 7*a*** shows a provisional connectivity diagram for the *C. borealis* STG. Although lobsters and crabs share many features of the gastric mill activity, there also appear to be some important differences. This raises the interesting possibility that different patterns of connectivity have evolved to produce similar motor patterns in different species. Moreover, at least in *C. borealis*, identified modulatory projection neurons are part of the circuitry that generates the gastric mill rhythm (22, 90, 126).

Work from the Nusbaum laboratory has characterized the effects of many different modulatory projection neurons in *C. borealis* (22, 41, 90, 93–98, 134, 135). Many projection neurons influence both the gastric and pyloric rhythms. For example, the modulatory commissural neuron 1 (MCN1) elicits a gastric mill rhythm whose period is an integer multiple of the pyloric rhythm period (132, 136). Moreover, under normal physiological conditions, interactions from the pyloric rhythm regulate MCN1's activity, thus establishing two different mechanisms by which the pyloric and gastric mill activity are coordinated (135).

NEURONS CAN SWITCH BETWEEN DIFFERENT CIRCUITS

For many years researchers thought that the pyloric and gastric mill circuits were separate circuits that showed relatively weak interactions among them, despite the presence of extensive synaptic interactions between pyloric and gastric neurons. However, we now know that, in the absence of gastric mill activity in crabs and some lobsters, neurons that usually are part of the gastric mill circuit fire in time with the pyloric rhythm (137, 138) (**Figure 7*b***). When these neurons fire in pyloric time, they can entrain and reset the pyloric rhythm (139). When the gastric mill rhythm is active and the neurons fire in time with the gastric mill rhythm, they can entrain and reset the gastric mill rhythm (139). Thus, gastric neurons genuinely switch between being members of the pyloric or gastric CPGs.

Interactions also exist when both rhythms are active. **Figure 7*c*** shows recordings from the same experiment as **Figure 7*b***, in this case during ongoing gastric activity. When both rhythms are active, pyloric neuron firing patterns can show substantial modulation over the gastric cycle, as seen in the prolonged interburst interval of the PD neuron at the onset of the LG burst (red bars in **Figure 7*c***). Gastric neurons can show substantial membrane potential modulation in pyloric time (blue arrow in **Figure 7*c***; see also **Figure 6**). Therefore, STG neurons express both patterns simultaneously to different degrees (139, 140). Such a description may be particularly useful because both gastric and pyloric muscles express both rhythms in the contractions they produce (137, 141).

In addition, neuromodulators can recruit neurons into new circuit configurations. In the spiny lobster, the neuromodulator red pigment concentrating hormone strongly potentiates the synapses between the IV neurons of the cardiac sac rhythm and neurons of the gastric mill rhythm. This results in a new network in which cardiac sac and gastric neurons are coordinately active (142). Similarly, activity of the PS neurons, the IV homologs in the lobster *H. gammarus*, produces a novel rhythm in which members of the gastric mill and pyloric networks participate (143, 144).

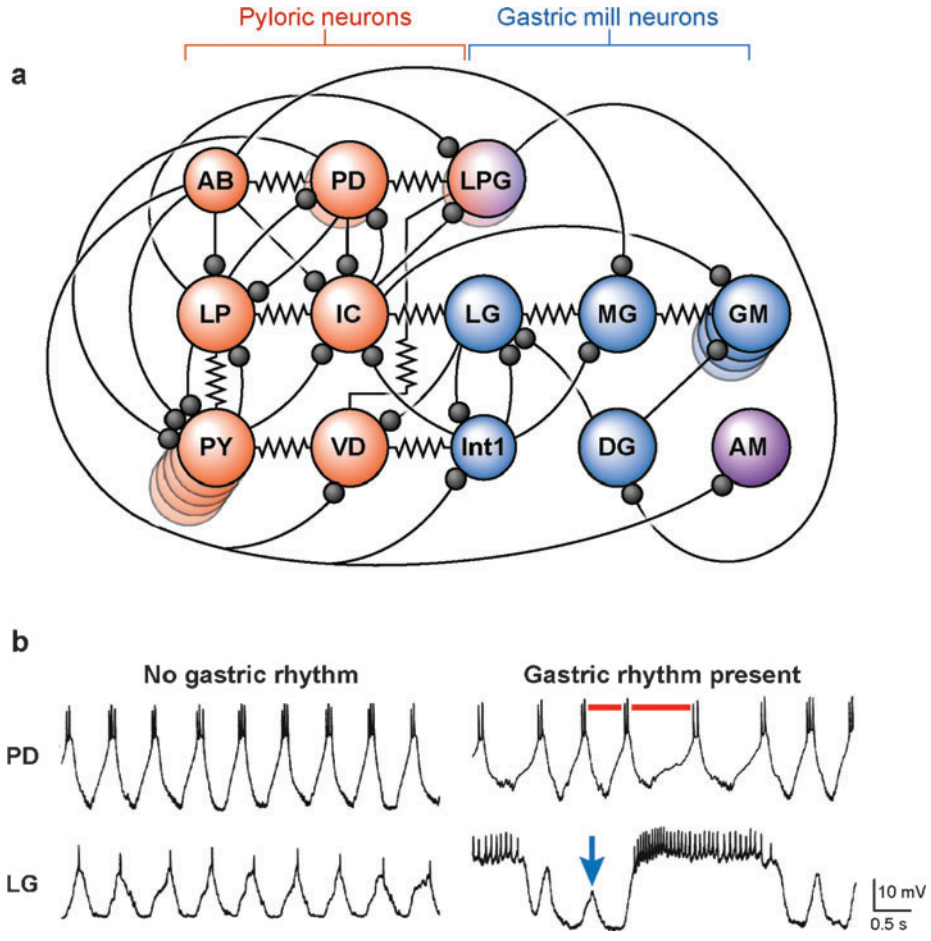


Figure 7

Interactions between the gastric mill and pyloric rhythms. (*a*) Provisional connectivity diagram of the STG neurons in *C. borealis* that shows the substantial synaptic connections between gastric mill circuit and pyloric circuit neurons. Neurons that innervate muscles of the pylorus [and the anterior burster (AB) interneuron] are shown in red, and neurons that innervate muscles of the gastric mill [and interneuron 1 (Int1)] are shown in blue. The lateral posterior ganglion (LPG) neurons innervate pyloric and gastric mill muscles, and the anterior median (AM) neuron innervates a cardiac sac muscle. Circles indicate inhibitory connections, and resistor symbols indicate electrical coupling. Modified from Reference 22. DG, dorsal gastric neuron; IC, inferior cardiac neuron; LG, lateral gastric neuron; LP, lateral pyloric neuron; MG, medial gastric neuron; PD, pyloric dilator neuron; VD, ventricular dilator neuron. (*b*) Intracellular recordings of the PD and LG neurons in *C. borealis*. In the absence of gastric mill activity, the LG neuron fires in time with the pyloric rhythm. In the presence of gastric mill activity, LG is active in gastric time but still shows membrane potential modulation in pyloric time (*blue arrow*). The pyloric rhythm slows down during the LG burst (*red bars*). Modified with permission from Reference 138.

SENSORY INPUT TO THE STOMATOGASTRIC GANGLION

Sensory input plays an important role in shaping the output of CPGs, and the STNS is no different from other motor systems in this regard. Various sensory neurons whose activity alters the pyloric and gastric mill neurons have been identified. Sensory feedback in motor systems is usually studied with respect to the control of timing and magnitude that it

exerts through connections with either motor neurons or CPG neurons (145). However, an important role of sensory feedback in the STNS seems to be the activation of and interaction with different descending neuromodulatory pathways (86, 96).

The posterior stomach receptors were the first mechanoreceptors to be described (146). These neurons influence the gastric and pyloric rhythms, presumably acting in the CoGs and other sites. The gastropyloric receptor (GPR) neurons are stretch receptors that innervate stomach muscles (29, 98, 147–153). They synapse directly on STG neurons (150) as well as project anteriorly to the CoGs, where they activate specific sets of descending projection neurons (98). Another stretch receptor, the anterior gastric neuron, has a bipolar soma just posterior to the STG and monitors stretch in the large gastric mill muscles but projects anteriorly without synapsing in the STG (99, 127, 154, 155). The ventral cardiac neurons are a recently described set of sensory neurons that act directly on modulatory projection neurons in the CoGs (95, 97). Interestingly, ventral cardiac neurons and GPRs elicit distinct gastric mill rhythms, although they both activate the same descending projection neurons, MCN1 and CPN2 (97, 98).

Substances present in the hemolymph, including serotonin and the neuropeptide allatostatin (147, 148), modulate the responses of the GPR neurons to muscle stretch. These substances not only alter the stretch responses but also influence the precision of their spiking.

DEVELOPMENT, MATURATION, AND GROWTH OF THE STOMATOGASTRIC GANGLION

In lobsters, the STG is present with its full constellation of neurons before the midpoint of embryonic development (156). At this time it is spontaneously active (156, 157) and generates a rhythm that drives the muscles of the embryonic stomach, including some that eventually become pyloric region muscles and others that eventually become gastric mill region muscles (156, 158). The existence of this seemingly conjoint rhythm, which combines members of the future gastric mill and pyloric networks during embryonic time, has several possible explanations. At one extreme, this may be another example of the neuromodulatory reconfiguration of the STG networks, and the embryonic system may be essentially similar to that of the adult, but in a different neuromodulatory state. Alternatively, the differences between the embryonic rhythm and those generated in the adult may result from differences in the synaptic and intrinsic properties of the neurons at these early stages.

Much of the neuromodulatory complement is formed quite early in development (159–163), although some neuromodulators do not become detectable until larval stages. The receptors for most, if not all, of the modulators that act in the adult appear to be present in the embryo (163–165; K. Rehm, unpublished observations).

Based on modeling work, the Meyrand laboratory has suggested that strong electrical coupling among the neurons in the embryonic network accounts for the fact that the future gastric mill neurons tend to fire in time with the future pyloric neurons (166). A descending projection in the embryo may be responsible for maintaining a high level of coupling (158, 166), which is later inhibited as the animals go through metamorphosis.

Lobsters undergo a final metamorphosis after their three larval stages. At this point they are still quite small, but these juveniles resemble the adult in body and stomach structure. Despite considerable changes in body and ganglion size, the STNS isolated from juveniles produces pyloric rhythms virtually indistinguishable from those seen in adults (105). Thus, there must be mechanisms in place to assure that network stability is maintained as individual neurons are adding membranes and synthesizing and inserting channels and as distances between synapses are changing.

HOMEOSTASIS AND RECOVERY OF FUNCTION

As described above, when the STG is isolated from its descending modulatory inputs, the gastric mill rhythm stops, and the pyloric rhythm usually also stops. Nonetheless, if the preparations are maintained in sterile conditions in vitro after one to several days, the pyloric rhythm resumes (**Figure 8**), now in the absence of neuromodulatory inputs (17, 102, 167–170), after a period in which the preparations generate bouts of intermittent activity (102). This recovery is blocked by inhibitors of mRNA synthesis (169), and is associated with increased excitability in the PD neurons (170). This recovery is consistent with the interpretation that neurons in the STG have a target activity level and mechanisms by which they can sense that activity and alter their channel densities accordingly (167, 171–174). STG neurons also may respond directly to the loss of neuromodulatory signals, which may trigger the changes that allow recovery of activity (168).

The hypothesis that neurons and networks have a target activity level and homeostatic mechanisms tending to maintain stable neuronal and network function predicts that overexpression of a current may result in compensatory changes in one or more other currents (171, 172). Injection of *shal* mRNA encoding I_A (15, 175) into PD neurons resulted in enhanced I_A current measured in voltage clamp but no obvious change in the firing pattern of the PD neurons (176). A compensatory upregulation of I_h explained the lack of change in excitability (176). However, the same upregulation of I_h occurred when an inactive form of the *shal* gene was expressed, arguing that a direct molecular mechanism, and not activity, mediated the compensatory change (176, 177). This coupling of the two currents was not reciprocal, as injection of the mRNA encoding I_h failed to alter I_A, and did result in altered patterns of activity (178).

Correlated expression of I_A and I_h was also seen in recent single-neuron, real-time PCR experiments from identified crab STG neurons (16). In this study, the values of these currents were tightly correlated with each other in a given PD neuron, but the values across preparations were highly variable. However, the values of these currents were very similar in the two electrically coupled PD neurons within a preparation. This may indicate that a small molecular metabolite is important for controlling the expression of these currents or that the two electrically coupled neurons

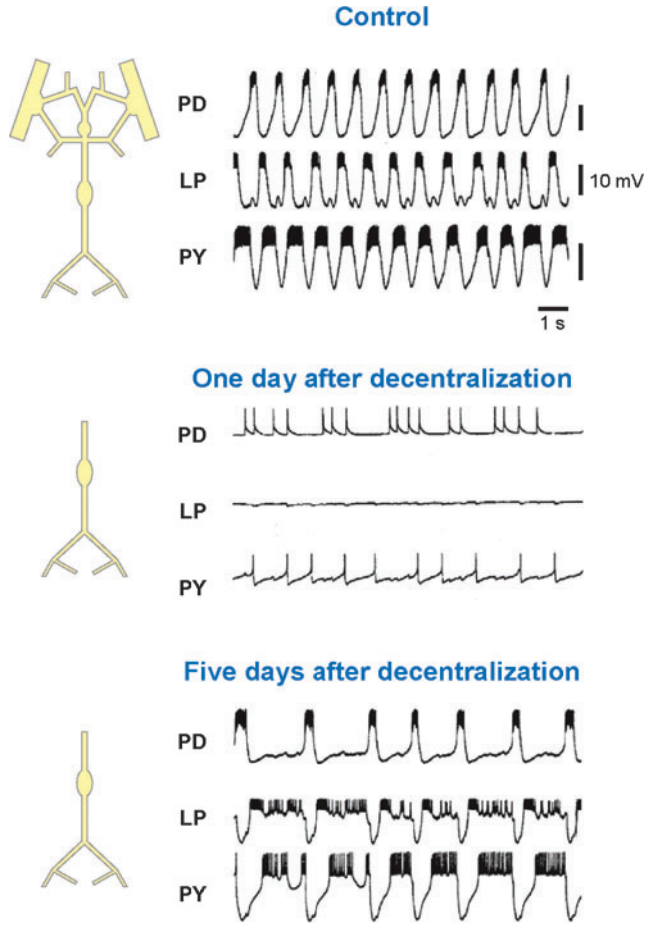


Figure 8

Recovery of the pyloric rhythm after decentralization in the lobster *Jasus lalandii*. The triphasic rhythmic activity seen in control lobsters (*top panel*) ceases after descending modulatory input is removed (*middle panel*). Rhythmic activity resumes after several days in the absence of modulatory input (*lower panel*). LP, lateral pyloric neuron; PD, pyloric dilator neuron; PY, pyloric neuron. Modified with permission from Reference 170.

within a given animal have very similar histories of activity (16).

The molecular identification of the genes for channels and receptors (15, 175, 179–188) opens the possibility of determining where ion channels and receptors are found over the complex structures of STG neurons. For example, different genes appear to contribute to A-type K^+ currents in different regions of neurons (179), and antibodies raised against different Ca^{2+} channels apparently also show differential distribution of labeling (187). Nonetheless, these studies provide only a starting point for understanding the extent to which STG neurons specifically localize both ion channels and receptors and to which this localization is modified by experience.

SUMMARY POINTS

1. Neurons and neural circuits are modulated by many substances that may act singly or in concert to reconfigure neuronal networks. The targets for neuromodulation include all neurons within a circuit and all the neurons' synapses.
2. A pacemaker kernel of three neurons drives the pyloric rhythm, which depends on a series of mechanisms to maintain approximately constant firing phases over a range of frequencies.
3. The gastric mill rhythm emerges from the connectivity among the gastric mill neurons and the activity of descending modulatory inputs. Different patterns of connectivity may subserve the production of similar gastric mill motor patterns in different species, and within the same species, different mechanisms may generate similar gastric mill motor patterns.
4. Individual neurons may fire in time with more than one rhythm and may switch among different pattern-generating circuits. Consequently, activity alone is not a sufficient criterion for neuronal identification, thus complicating the identification of circuit neurons in larger vertebrate systems.
5. Sensory modification of the STG motor patterns results both from direct projections to the STG and from the activation of specific sets of descending modulatory projections. Sensory neurons themselves are subject to neuromodulation that alters their response to stretch.
6. The STG is fully formed early in development but generates motor patterns different from those in the adult.
7. If the STG is deprived of its normal constellation of neuromodulatory inputs for 24–72 h, activity resumes independently of those neuromodulatory inputs. Thus, there are mechanisms that maintain stable network output under different physiological conditions.
8. There may be multiple combinations of conductance densities consistent with the activity patterns of individual identified neurons. The expression of some channel genes may be coupled, resulting in mechanisms for compensation for changes in some currents.

FUTURE ISSUES

1. What kinds of mechanisms stabilize constant performance of the pyloric and gastric mill networks over many years, despite ongoing channel turnover and considerable growth of the neurons and the biomechanical plant that they drive?
2. If every synapse and neuron in a network is subject to neuromodulation, what prevents overmodulation and keeps networks in the appropriate operating range?
3. What combinations of membrane conductances give rise to the specific properties of the different classes of identified neurons? What specifies neuronal identity at the molecular level?

LITERATURE CITED

1. Maynard DM. 1972. Simpler networks. *Ann. N.Y. Acad. Sci*. 193:59–72
2. Harris-Warrick RM, Marder E. 1991. Modulation of neural networks for behavior. *Annu. Rev. Neurosci*. 14:39–57
3. Hartline DK, Russell DF, Raper JA, Graubard K. 1988. Special cellular and synaptic mechanisms in motor pattern generation. *Comp. Biochem. Physiol.* 91C:115–31
4. Selverston AI, Russell DF, Miller JP, King DG. 1976. The stomatogastric nervous system: structure and function of a small neural network. *Prog. Neurobiol*. 7:215–90
5. Harris-Warrick RM, Marder E, Selverston AI, Moulins M. 1992. *Dynamic Biological Networks. The Stomatogastric Nervous System*. Cambridge, MA: MIT Press. 328 pp.
6. Selverston AI, Moulins M, eds. 1987. *The Crustacean Stomatogastric System*. Berlin: Springer-Verlag. 338 pp.
7. Meyrand P, Faumont S, Simmers J, Christie AE, Nusbaum MP. 2000. Species-specific modulation of pattern-generating circuits. *Eur. J. Neurosci*. 12:2585–96
8. Clemens S, Combes D, Meyrand P, Simmers J. 1998. Long-term expression of two interacting motor pattern-generating networks in the stomatogastric system of freely behaving lobster. *J. Neurophysiol*. 79:1396–408
9. Rezer E, Moulins M. 1983. Expression of the crustacean pyloric pattern generator in the intact animal. *J. Comp. Physiol. A* 153:17–28
10. Heinzel HG. 1988. Gastric mill activity in the lobster. II. Proctolin and octopamine initiate and modulate chewing. *J. Neurophysiol*. 59:551–65
11. Heinzel HG. 1988. Gastric mill activity in the lobster. I. Spontaneous modes of chewing. *J. Neurophysiol*. 59:528–50
12. Heinzel HG, Selverston AI. 1988. Gastric mill activity in the lobster. III. Effects of proctolin on the isolated central pattern generator. *J. Neurophysiol*. 59:566–85
13. Marder E, Calabrese RL. 1996. Principles of rhythmic motor pattern generation. *Physiol. Rev*. 76:687–717
14. Marder E. 1976. Cholinergic motor neurones in the stomatogastric system of the lobster. *J. Physiol*. 257:63–86
15. Baro DJ, Levini RM, Kim MT, Willms AR, Lanning CC, et al. 1997. Quantitative single-cell-reverse transcription-PCR demonstrates that A-current magnitude varies as a linear function of *shal* gene expression in identified stomatogastric neurons. *J. Neurosci.* 17:6597–10
16. Schulz DJ, Goaillard JM, Marder E. 2006. Variable channel expression in identified single and electrically coupled neurons in different animals. *Nat. Neurosci*. 9:356–62

17. Mizrahi A, Dickinson PS, Kloppenburg P, Fénelon V, Baro DJ, et al. 2001. Long-term maintenance of channel distribution in a central pattern generator neuron by neuromodulatory inputs revealed by decentralization in organ culture. *J. Neurosci.* 21:7331–39
18. Kiehn O, Butt SJ. 2003. Physiological, anatomical and genetic identification of CPG neurons in the developing mammalian spinal cord. *Prog. Neurobiol.* 70:347–61
19. Sugino K, Hempel CM, Miller MN, Hattox AM, Shapiro P, et al. 2006. Molecular taxonomy of major neuronal classes in the adult mouse forebrain. *Nat. Neurosci.* 9:99–107
20. Maynard DM, Dando MR. 1974. The structure of the stomatogastric neuromuscular system in *Callinectes sapidus*, *Homarus americanus* and *Panulirus argus* (decapoda crustacea). *Philos. Trans. R. Soc. London Ser. B* 268:161–220
21. Coleman MJ, Nusbaum MP, Cournil I, Claiborne BJ. 1992. Distribution of modulatory inputs to the stomatogastric ganglion of the crab, *Cancer borealis*. *J. Comp. Neurol.* 325:581–94
22. Nusbaum MP, Beenhakker MP. 2002. A small-systems approach to motor pattern generation. *Nature* 417:343–50
23. Kilman VL, Marder E. 1996. Ultrastructure of the stomatogastric ganglion neuropil of the crab, *Cancer borealis*. *J. Comp. Neurol.* 374:362–75
24. Bucher D, Johnson CD, Marder E. 2006. Neuronal morphology and neuropil structure in the stomatogastric ganglion of the lobster, *Homarus americanus*. *J. Comp. Neurol.* In press
25. King DG. 1976. Organization of crustacean neuropil. I. Patterns of synaptic connections in lobster stomatogastric ganglion. *J. Neurocytol.* 5:207–37
26. King DG. 1976. Organization of crustacean neuropil. II. Distribution of synaptic contacts on identified motor neurons in lobster stomatogastric ganglion. *J. Neurocytol.* 5:239–66
27. Marder E, Eisen JS. 1984. Transmitter identification of pyloric neurons: electrically coupled neurons use different neurotransmitters. *J. Neurophysiol.* 51:1345–61
28. Lingle C. 1980. The sensitivity of decapod foregut muscles to acetylcholine and glutamate. *J. Comp. Physiol.* 138:187–99
29. Katz PS, Eigg MH, Harris-Warrick RM. 1989. Serotonergic/cholinergic muscle receptor cells in the crab stomatogastric nervous system. I. Identification and characterization of the gastropyloric receptor cells. *J. Neurophysiol.* 62:558–70
30. Marder E, Bucher D. 2001. Central pattern generators and the control of rhythmic movements. *Curr. Biol.* 11:R986–96
31. Nusbaum MP, Blitz DM, Swensen AM, Wood D, Marder E. 2001. The roles of cotransmission in neural network modulation. *Trends Neurosci.* 24:146–54
32. Christie AE, Cain SD, Edwards JM, Clason TA, Cherny E, et al. 2004. The anterior cardiac plexus: an intrinsic neurosecretory site within the stomatogastric nervous system of the crab *Cancer productus*. *J. Exp. Biol.* 207:1163–82
33. Christie AE, Skiebe P, Marder E. 1995. Matrix of neuromodulators in neurosecretory structures of the crab, *Cancer borealis*. *J. Exp. Biol.* 198:2431–39
34. Barker DL, Kushner PD, Hooper NK. 1979. Synthesis of dopamine and octopamine in the crustacean stomatogastric nervous system. *Brain Res.* 161:99–113
35. Kushner PD, Maynard EA. 1977. Localization of monoamine fluorescence in the stomatogastric nervous system of lobsters. *Brain Res.* 129:13–28
36. Beltz B, Eisen JS, Flamm R, Harris-Warrick RM, Hooper S, Marder E. 1984. Serotonergic innervation and modulation of the stomatogastric ganglion of three decapod crustaceans (*Panulirus interruptus*, *Homarus americanus* and *Cancer irroratus)*. *J. Exp. Biol.* 109:35–54

37. Nusbaum MP, Marder E. 1989. A modulatory proctolin-containing neuron (MPN). I. Identification and characterization. *J. Neurosci*. 9:1591–99
38. Skiebe P, Schneider H. 1994. Allatostatin peptides in the crab stomatogastric nervous system: inhibition of the pyloric motor pattern and distribution of allatostatin-like immunoreactivity. *J. Exp. Biol*. 194:195–208
39. Li L, Kelley WP, Billimoria CP, Christie AE, Pulver SR, et al. 2003. Mass spectrometric investigation of the neuropeptide complement and release in the pericardial organs of the crab, *Cancer borealis*. *J. Neurochem*. 87:642–56
40. Stemmler EA, Provencher HL, Guiney ME, Gardner NP, Dickinson PS. 2005. Matrix-assisted laser desorption/ionization fourier transform mass spectrometry for the identification of orcokinin neuropeptides in crustaceans using metastable decay and sustained off-resonance irradiation. *Anal. Chem*. 77:3594–606
41. Blitz DM, Christie AE, Coleman MJ, Norris BJ, Marder E, Nusbaum MP. 1999. Different proctolin neurons elicit distinct motor patterns from a multifunctional neuronal network. *J. Neurosci*. 19:5449–63
42. Turrigiano GG, Selverston AI. 1990. A cholecystokinin-like hormone activates a feeding-related neural circuit in lobster. *Nature* 344:866–68
43. Dircksen H. 1998. Conserved crustacean cardioactive peptide: neural networks and function in arthropod evolution. In *Arthropod Endocrinology: Perspectives and Recent Advances*, ed. GM Coast, SG Webster, pp. 302–33. Cambridge, UK: Cambridge Univ. Press
44. Keller R. 1992. Crustacean neuropeptides: structures, functions and comparative aspects. *Experientia* 48:439–48
45. Hartline DK. 1979. Pattern generation in the lobster (*Panulirus*) stomatogastric ganglion. II. Pyloric network simulation. *Biol. Cybern*. 33:223–36
46. Hartline DK, Gassie DV Jr. 1979. Pattern generation in the lobster (*Panulirus*) stomatogastric ganglion. I. Pyloric neuron kinetics and synaptic interactions. *Biol. Cybern*. 33:209–22
47. Miller JP, Selverston AI. 1982. Mechanisms underlying pattern generation in lobster stomatogastric ganglion as determined by selective inactivation of identified neurons. IV. Network properties of pyloric system. *J. Neurophysiol*. 48:1416–32
48. Miller JP, Selverston AI. 1982. Mechanisms underlying pattern generation in lobster stomatogastric ganglion as determined by selective inactivation of identified neurons. II. Oscillatory properties of pyloric neurons. *J. Neurophysiol*. 48:1378–91
49. Selverston AI, Miller JP. 1980. Mechanisms underlying pattern generation in the lobster stomatogastric ganglion as determined by selective inactivation of identified neurons. I. Pyloric neurons. *J. Neurophysiol*. 44:1102–21
50. Grillner S. 2003. The motor infrastructure: from ion channels to neuronal networks. *Nat. Rev. Neurosci*. 4:573–86
51. Rekling JC, Feldman JL. 1998. PreBötzinger complex and pacemaker neurons: hypothesized site and kernel for respiratory rhythm generation. *Annu. Rev. Physiol*. 60:385–405
52. Ramirez JM, Tryba AK, Pena F. 2004. Pacemaker neurons and neuronal networks: an integrative view. *Curr. Opin. Neurobiol*. 14:665–74
53. Kiehn O. 2006. Locomotor circuits in the mammalian spinal cord. *Annu. Rev. Neurosci*. 29:279–306
54. Marder E, Paupardin-Tritsch D. 1978. The pharmacological properties of some crustacean neuronal acetylcholine, gamma-aminobutyric acid and L-glutamate responses. *J. Physiol*. 280:213–36

55. Eisen JS, Marder E. 1982. Mechanisms underlying pattern generation in lobster stomatogastric ganglion as determined by selective inactivation of identified neurons. III. Synaptic connections of electrically coupled pyloric neurons. *J. Neurophysiol.* 48:1392–415
56. Miller JP, Selverston A. 1979. Rapid killing of single neurons by irradiation of intracellularly injected dye. *Science* 206:702–4
57. Elson RC, Huerta R, Abarbanel HD, Rabinovich MI, Selverston AI. 1999. Dynamic control of irregular bursting in an identified neuron of an oscillatory circuit. *J. Neurophysiol.* 82:115–22
58. Szucs A, Pinto RD, Rabinovich MI, Abarbanel HD, Selverston AI. 2003. Synaptic modulation of the interspike interval signatures of bursting pyloric neurons. *J. Neurophysiol.* 89:1363–77
59. Marder E, Eisen JS. 1984. Electrically coupled pacemaker neurons respond differently to the same physiological inputs and neurotransmitters. *J. Neurophysiol.* 51:1362–74
60. Harris-Warrick RM, Coniglio LM, Levini RM, Gueron S, Guckenheimer J. 1995. Dopamine modulation of two subthreshold currents produces phase shifts in activity of an identified motoneuron. *J. Neurophysiol.* 74:1404–20
61. Eisen JS, Marder E. 1984. A mechanism for production of phase shifts in a pattern generator. *J. Neurophysiol.* 51:1375–93
62. Rabbah P, Nadim F. 2005. Synaptic dynamics do not determine proper phase of activity in a central pattern generator. *J. Neurosci.* 25:11269–78
63. Marder E, Thirumalai V. 2002. Cellular, synaptic and network effects of neuromodulation. *Neural Netw.* 15:479–93
64. Flamm RE, Harris-Warrick RM. 1986. Aminergic modulation in lobster stomatogastric ganglion. I. Effects on motor pattern and activity of neurons within the pyloric circuit. *J. Neurophysiol.* 55:847–65
65. Hooper SL, Marder E. 1987. Modulation of the lobster pyloric rhythm by the peptide proctolin. *J. Neurosci.* 7:2097–112
66. Nusbaum MP, Marder E. 1988. A neuronal role for a crustacean red pigment concentrating hormone-like peptide: neuromodulation of the pyloric rhythm in the crab, *Cancer borealis*. *J. Exp. Biol.* 135:165–81
67. Weimann JM, Skiebe P, Heinzel H-G, Soto C, Kopell N, et al. 1997. Modulation of oscillator interactions in the crab stomatogastric ganglion by crustacean cardioactive peptide. *J. Neurosci.* 17:1748–60
68. Turrigiano GG, Selverston AI. 1989. Cholecystokinin-like peptide is a modulator of a crustacean central pattern generator. *J. Neurosci.* 9:2486–501
69. Weimann JM, Marder E, Evans B, Calabrese RL. 1993. The effects of SDRNFLRFamide and TNRNFLRFamide on the motor patterns of the stomatogastric ganglion of the crab *Cancer borealis*. *J. Exp. Biol.* 181:1–26
70. Scholz NL, de Vente J, Truman JW, Graubard K. 2001. Neural network partitioning by NO and cGMP. *J. Neurosci.* 21:1610–18
71. Christie AE, Stemmler EA, Peguero B, Messinger DI, Provencher HL, et al. 2006. Identification, physiological actions, and distribution of VYRKPPFNGSIFamide (Val1-SIFamide) in the stomatogastric nervous system of the American lobster *Homarus americanus*. *J. Comp. Neurol.* 496:406–21
72. Claiborne B, Selverston A. 1984. Histamine as a neurotransmitter in the stomatogastric nervous system of the spiny lobster. *J. Neurosci.* 4:708–21
73. Swensen AM, Golowasch J, Christie AE, Coleman MJ, Nusbaum MP, Marder E. 2000. GABA and responses to GABA in the stomatogastric ganglion of the crab *Cancer borealis*. *J. Exp. Biol.* 203:2075–92

74. Swensen AM, Marder E. 2000. Multiple peptides converge to activate the same voltage-dependent current in a central pattern-generating circuit. *J. Neurosci*. 20:6752–59
75. Marder E, Hooper SL. 1985. Neurotransmitter modulation of the stomatogastric ganglion of decapod crustaceans. In *Model Neural Networks and Behavior*, ed. AI Selverston, pp. 319–37. New York: Plenum Press
76. Marder E, Weimann JM. 1992. Modulatory control of multiple task processing in the stomatogastric nervous system. In *Neurobiology of Motor Progamme Selection*, ed. J Kien, C McCrohan, B Winlow, pp. 3–19. New York: Pergamon Press
77. Kiehn O, Harris-Warrick RM. 1992. 5-HT modulation of hyperpolarization-activated inward current and calcium-dependent outward current in a crustacean motor neuron. *J. Neurophysiol*. 68:496–508
78. Harris-Warrick RM, Johnson BR, Peck JH, Kloppenburg P, Ayali A, Skarbinski J. 1998. Distributed effects of dopamine modulation in the crustacean pyloric network. *Ann. N.Y. Acad. Sci*. 860:155–67
79. Flamm RE, Harris-Warrick RM. 1986. Aminergic modulation in lobster stomatogastric ganglion. II. Target neurons of dopamine, octopamine, and serotonin within the pyloric circuit. *J. Neurophysiol*. 55:866–81
80. Johnson BR, Peck JH, Harris-Warrick RM. 1995. Distributed amine modulation of graded chemical transmission in the pyloric network of the lobster stomatogastric ganglion. *J. Neurophysiol*. 174:437–52
81. Gruhn M, Guckenheimer J, Land B, Harris-Warrick RM. 2005. Dopamine modulation of two delayed rectifier potassium currents in a small neural network. *J. Neurophysiol*. 94:2888–900
82. Kloppenburg P, Levini RM, Harris-Warrick RM. 1999. Dopamine modulates two potassium currents and inhibits the intrinsic firing properties of an identified motor neuron in a central pattern generator network. *J. Neurophysiol*. 81:29–38
83. Harris-Warrick RM, Coniglio LM, Barazangi N, Guckenheimer J, Gueron S. 1995. Dopamine modulation of transient potassium current evokes phase shifts in a central pattern generator network. *J. Neurosci*. 15:342–58
84. Golowasch J, Marder E. 1992. Proctolin activates an inward current whose voltage dependence is modified by extracellular Ca^{2+}. *J. Neurosci*. 12:810–17
85. Dando MR, Selverston AI. 1972. Command fibres from the supraesophageal ganglion to the stomatogastric ganglion in *Panulirus argus*. *J. Comp. Physiol*. 78:138–75
86. Sigvardt KA, Mulloney B. 1982. Sensory alteration of motor patterns in the stomatogastric nervous system of the spiny lobster *Panulirus interruptus*. *J. Exp. Biol*. 97:137–52
87. Sigvardt KA, Mulloney B. 1982. Properties of synapses made by IVN command-interneurones in the stomatogastric ganglion of the spiny lobster *Panulirus interruptus*. *J. Exp. Biol*. 97:153–68
88. Dickinson PS, Nagy F. 1983. Control of a central pattern generator by an identified modulatory interneurone in crustacea. II. Induction and modification of plateau properties in pyloric neurones. *J. Exp. Biol*. 105:59–82
89. Nagy F, Dickinson PS. 1983. Control of a central pattern generator by an identified modulatory interneurone in crustacea. I. Modulation of the pyloric motor output. *J. Exp. Biol*. 105:33–58
90. Coleman MJ, Meyrand P, Nusbaum MP. 1995. A switch between two modes of synaptic transmission mediated by presynaptic inhibition. *Nature* 378:502–5
91. Coleman MJ, Nusbaum MP. 1994. Functional consequences of compartmentalization of synaptic input. *J. Neurosci*. 14:6544–52

92. Christie AE, Stein W, Quinlan JE, Beenhakker MP, Marder E, Nusbaum MP. 2004. Actions of a histaminergic/peptidergic projection neuron on rhythmic motor patterns in the stomatogastric nervous system of the crab *Cancer borealis*. *J. Comp. Neurol*. 469:153–69
93. Blitz DM, Nusbaum MP. 1999. Distinct functions for cotransmitters mediating motor pattern selection. *J. Neurosci*. 19:6774–83
94. Wood DE, Stein W, Nusbaum MP. 2000. Projection neurons with shared cotransmitters elicit different motor patterns from the same neuronal circuit. *J. Neurosci*. 20:8943–53
95. Beenhakker MP, Blitz DM, Nusbaum MP. 2004. Long-lasting activation of rhythmic neuronal activity by a novel mechanosensory system in the crustacean stomatogastric nervous system. *J. Neurophysiol*. 91:78–91
96. Beenhakker MP, DeLong ND, Saideman SR, Nadim F, Nusbaum MP. 2005. Proprioceptor regulation of motor circuit activity by presynaptic inhibition of a modulatory projection neuron. *J. Neurosci*. 25:8794–806
97. Beenhakker MP, Nusbaum MP. 2004. Mechanosensory activation of a motor circuit by coactivation of two projection neurons. *J. Neurosci*. 24:6741–50
98. Blitz DM, Beenhakker MP, Nusbaum MP. 2004. Different sensory systems share projection neurons but elicit distinct motor patterns. *J. Neurosci*. 24:11381–90
99. Combes D, Meyrand P, Simmers J. 1999. Motor pattern specification by dual descending pathways to a lobster rhythm-generating network. *J. Neurosci*. 19:3610–19
100. Hooper SL. 1997. Phase maintenance in the pyloric pattern of the lobster (*Panulirus interruptus*) stomatogastric ganglion. *J. Comput. Neurosci*. 4:191–205
101. Hooper SL. 1997. The pyloric pattern of the lobster (*Panulirus interruptus*) stomatogastric ganglion comprises two phase maintaining subsets. *J. Comput. Neurosci*. 4:207–19
102. Luther JA, Robie AA, Yarotsky J, Reina C, Marder E, Golowasch J. 2003. Episodic bouts of activity accompany recovery of rhythmic output by a neuromodulator- and activity-deprived adult neural network. *J. Neurophysiol*. 90:2720–30
103. Manor Y, Bose A, Booth V, Nadim F. 2003. Contribution of synaptic depression to phase maintenance in a model rhythmic network. *J. Neurophysiol*. 90:3513–28
104. Greenberg I, Manor Y. 2005. Synaptic depression in conjunction with A-current channels promote phase constancy in a rhythmic network. *J. Neurophysiol*. 93:656–77
105. Bucher D, Prinz AA, Marder E. 2005. Animal-to-animal variability in motor pattern production in adults and during growth. *J. Neurosci*. 25:1611–19
106. Graubard K. 1978. Synaptic transmission without action potentials: input-output properties of a nonspiking presynaptic neuron. *J. Neurophysiol*. 41:1014–25
107. Graubard K, Raper JA, Hartline DK. 1980. Graded synaptic transmission between spiking neurons. *Proc. Natl. Acad. Sci. USA* 77:3733–35
108. Manor Y, Nadim F, Abbott LF, Marder E. 1997. Temporal dynamics of graded synaptic transmission in the lobster stomatogastric ganglion. *J. Neurosci*. 17:5610–21
109. Mamiya A, Manor Y, Nadim F. 2003. Short-term dynamics of a mixed chemical and electrical synapse in a rhythmic network. *J. Neurosci*. 23:9557–64
110. Tierney AJ, Harris-Warrick RM. 1992. Physiological role of the transient potassium current in the pyloric circuit of the lobster stomatogastric ganglion. *J. Neurophysiol*. 67:599–609
111. Kepler TB, Marder E, Abbott LF. 1990. The effect of electrical coupling on the frequency of model neuronal oscillators. *Science* 248:83–85
112. Soto-Trevino C, Rabbah P, Marder E, Nadim F. 2005. Computational model of electrically coupled, intrinsically distinct pacemaker neurons. *J. Neurophysiol*. 94:590–604
113. Nadim F, Manor Y, Kopell N, Marder E. 1999. Synaptic depression creates a switch that controls the frequency of an oscillatory circuit. *Proc. Natl. Acad. Sci. USA* 96:8206–11

114. Ayali A, Harris-Warrick RM. 1999. Monoamine control of the pacemaker kernel and cycle frequency in the lobster pyloric network. *J. Neurosci*. 19:6712–22
115. Ayers JL, Selverston AI. 1979. Monosynaptic entrainment of an endogenous pacemaker network: a cellular mechanism for von Holt's magnet effect. *J. Comp. Physiol*. 129:5–17
116. Prinz AA, Thirumalai V, Marder E. 2003. The functional consequences of changes in the strength and duration of synaptic inputs to oscillatory neurons. *J. Neurosci*. 23:943–54
117. Thirumalai V, Prinz AA, Johnson CD, Marder E. 2006. Red pigment concentrating hormone strongly enhances the strength of the feedback to the pyloric rhythm oscillator but has little effect on pyloric rhythm period. *J. Neurophysiol*. 95:1762–70
118. Bal T, Nagy F, Moulins M. 1994. Muscarinic modulation of a pattern-generating network: control of neuronal properties. *J. Neurosci*. 14:3019–35
119. Harris-Warrick RM, Flamm RE. 1987. Multiple mechanisms of bursting in a conditional bursting neuron. *J. Neurosci*. 7:2113–28
120. Epstein IR, Marder E. 1990. Multiple modes of a conditional neural oscillator. *Biol. Cybern*. 63:25–34
121. Goldman MS, Golowasch J, Marder E, Abbott LF. 2001. Global structure, robustness, and modulation of neuronal models. *J. Neurosci*. 21:5229–38
122. Guckenheimer J, Gueron S, Harris-Warrick RM. 1993. Mapping the dynamics of a bursting neuron. *Philos. Trans. R. Soc. London Ser. B* 341:345–59
123. Taylor AL, Hickey TJ, Prinz AA, Marder E. 2006. Structure and visualization of high-dimensional conductance spaces. *J. Neurophysiol*. 96:891–905
124. Clemens S, Massabuau JC, Legeay A, Meyrand P, Simmers J. 1998. In vivo modulation of interacting central pattern generators in lobster stomatogastric ganglion: influence of feeding and partial pressure of oxygen. *J. Neurosci*. 18:2788–99
125. Clemens S, Meyrand P, Simmers J. 1998. Feeding-induced changes in temporal patterning of muscle activity in the lobster stomatogastric system. *Neurosci. Lett*. 254:65–68
126. Norris BJ, Coleman MJ, Nusbaum MP. 1994. Recruitment of a projection neuron determines gastric mill motor pattern selection in the stomatogastric nervous system of the crab, *Cancer borealis*. *J. Neurophysiol*. 72:1451–63
127. Combes D, Meyrand P, Simmers J. 1999. Dynamic restructuring of a rhythmic motor program by a single mechanorecptor neuron in lobster. *J. Neurosci*. 19:3620–28
128. Mulloney B, Selverston AI. 1974. Organization of the stomatogastric ganglion in the spiny lobster. I. Neurons driving the lateral teeth. *J. Comp. Physiol*. 91:1–32
129. Mulloney B, Selverston AI. 1974. Organization of the stomatogastric ganglion in the spiny lobster. III. Coordination of the two subsets of the gastric system. *J. Comp. Physiol*. 91:53–78
130. Dickinson PS, Nagy F, Moulins M. 1988. Control of central pattern generators by an identified neurone in crustacea: activation of the gastric mill motor pattern by a neurone known to modulate the pyloric network. *J. Exp. Biol*. 136:53–87
131. Selverston AI, Mulloney B. 1974. Organization of the stomatogastric ganglion of the spiny lobster. II. Neurons driving the medial tooth. *J. Comp. Physiol*. 91:33–51
132. Bartos M, Manor Y, Nadim F, Marder E, Nusbaum MP. 1999. Coordination of fast and slow rhythmic neuronal circuits. *J. Neurosci*. 19:6650–60
133. Bartos M, Nusbaum MP. 1997. Intercircuit control of motor pattern modulation by presynaptic inhibition. *J. Neurosci*. 17:2247–56
134. Blitz DM, Nusbaum MP. 1997. Motor pattern selection via inhibition of parallel pathways. *J. Neurosci*. 17:4965–75
135. Wood DE, Manor Y, Nadim F, Nusbaum MP. 2004. Intercircuit control via rhythmic regulation of projection neuron activity. *J. Neurosci*. 24:7455–63

136. Nadim F, Manor Y, Nusbaum MP, Marder E. 1998. Frequency regulation of a slow rhythm by a fast periodic input. *J. Neurosci*. 18:5053–67
137. Heinzel HG, Weimann JM, Marder E. 1993. The behavioral repertoire of the gastric mill in the crab, *Cancer pagurus*: an in situ endoscopic and electrophysiological examination. *J. Neurosci*. 13:1793–803
138. Weimann JM, Meyrand P, Marder E. 1991. Neurons that form multiple pattern generators: identification and multiple activity patterns of gastric/pyloric neurons in the crab stomatogastric system. *J. Neurophysiol*. 65:111–22
139. Weimann JM, Marder E. 1994. Switching neurons are integral members of multiple oscillatory networks. *Curr. Biol*. 4:896–902
140. Bucher D, Taylor AL, Marder E. 2006. Central pattern generating neurons simultaneously express fast and slow rhythmic activities in the stomatogastric ganglion. *J. Neurophysiol*. 95:3617–32
141. Thuma JB, Morris LG, Weaver AL, Hooper SL. 2003. Lobster (*Panulirus interruptus*) pyloric muscles express the motor patterns of three neural networks, only one of which innervates the muscles. *J. Neurosci*. 23:8911–20
142. Dickinson PS, Mecsas C, Marder E. 1990. Neuropeptide fusion of two motor pattern generator circuits. *Nature* 344:155–58
143. Meyrand P, Simmers J, Moulins M. 1991. Construction of a pattern-generating circuit with neurons of different networks. *Nature* 351:60–63
144. Meyrand P, Simmers J, Moulins M. 1994. Dynamic construction of a neural network from multiple pattern generators in the lobster stomatogastric nervous system. *J. Neurosci*. 14:630–44
145. Büschges A. 2005. Sensory control and organization of neural networks mediating coordination of multisegmental organs for locomotion. *J. Neurophysiol*. 93:1127–35
146. Dando MR, Laverack MS. 1969. The anatomy and physiology of the posterior stomach nerve (p.s.n.) in some decapod crustacea. *Proc. R. Soc. London Ser. B* 171:465–82
147. Billimoria CP, DiCaprio RA, Birmingham JT, Abbott LF, Marder E. 2006. Neuromodulation of spike-timing precision in sensory neurons. *J. Neurosci*. 26:5910–19
148. Birmingham JT, Billimoria CP, DeKlotz TR, Stewart RA, Marder E. 2003. Differential and history-dependent modulation of a stretch receptor in the stomatogastric system of the crab, *Cancer borealis*. *J. Neurophysiol*. 90:3608–16
149. Birmingham JT, Szuts Z, Abbott LF, Marder E. 1999. Encoding of muscle movement on two time scales by a sensory neuron that switches between spiking and burst modes. *J. Neurophysiol*. 82:2786–97
150. Katz PS, Harris-Warrick RM. 1989. Serotonergic/cholinergic muscle receptor cells in the crab stomatogastric nervous system. II. Rapid nicotinic and prolonged modulatory effects on neurons in the stomatogastric ganglion. *J. Neurophysiol*. 62:571–81
151. Katz PS, Harris-Warrick RM. 1990. Neuromodulation of the crab pyloric central pattern generator by serotonergic/cholinergic proprioceptive afferents. *J. Neurosci*. 10:1495–512
152. Katz PS, Harris-Warrick RM. 1990. Actions of identified neuromodulatory neurons in a simple motor system. *Trends Neurosci*. 13:367–73
153. Katz PS, Harris-Warrick RM. 1991. Recruitment of crab gastric mill neurons into the pyloric motor pattern by mechanosensory afferent stimulation. *J. Neurophysiol*. 65:1442–51
154. Combes D, Simmers AJ, Moulins M. 1995. Structural and functional characterization of a muscle tendon proprioceptor in lobster. *J. Comp. Neurol*. 363:221–34
155. Combes D, Simmers AJ, Moulins M. 1997. Conditional dendritic oscillators in a lobster mechanoreceptor neurone. *J. Physiol*. 499:161–77

156. Casasnovas B, Meyrand P. 1995. Functional differentiation of adult neural circuits from a single embryonic network. *J. Neurosci*. 15:5703–18
157. Richards KS, Miller WL, Marder E. 1999. Maturation of the rhythmic activity produced by the stomatogastric ganglion of the lobster, *Homarus americanus*. *J. Neurophysiol*. 82:2006–9
158. Le Feuvre Y, Fénelon VS, Meyrand P. 1999. Unmasking of multiple adult neural networks from a single embryonic circuit by removal of neuromodulatory inputs. *Nature* 402:660–64
159. Fénelon V, Casasnovas B, Faumont S, Meyrand P. 1998. Ontogenetic alteration in peptidergic expression within a stable neuronal population in lobster stomatogastric nervous system. *J. Comp. Neurol*. 399:289–305
160. Fénelon VS, Kilman V, Meyrand P, Marder E. 1999. Sequential developmental acquisition of neuromodulatory inputs to a central pattern-generating network. *J. Comp. Neurol*. 408:335–51
161. Kilman VL, Fénelon V, Richards KS, Thirumalai V, Meyrand P, Marder E. 1999. Sequential developmental acquisition of cotransmitters in identified sensory neurons of the stomatogastric nervous system of the lobsters, *Homarus americanus* and *Homarus gammarus*. *J. Comp. Neurol*. 408:318–34
162. Pulver SR, Marder E. 2002. Neuromodulatory complement of the pericardial organs in the embryonic lobster, *Homarus americanus*. *J. Comp. Neurol*. 451:79–90
163. Pulver SR, Thirumalai V, Richards KS, Marder E. 2003. Dopamine and histamine in the developing stomatogastric system of the lobster *Homarus americanus*. *J. Comp. Neurol*. 462:400–14
164. Richards KS, Marder E. 2000. The actions of crustacean cardioactive peptide on adult and developing stomatogastric ganglion motor patterns. *J. Neurobiol*. 44:31–44
165. Richards KS, Simon DJ, Pulver SR, Beltz BS, Marder E. 2003. Serotonin in the developing stomatogastric system of the lobster, *Homarus americanus*. *J. Neurobiol*. 54:380–92
166. Bem T, Le Feuvre Y, Simmers J, Meyrand P. 2002. Electrical coupling can prevent expression of adult-like properties in an embryonic neural circuit. *J. Neurophysiol*. 87:538–47
167. Golowasch J, Casey M, Abbott LF, Marder E. 1999. Network stability from activity-dependent regulation of neuronal conductances. *Neural Comput*. 11:1079–96
168. Thoby-Brisson M, Simmers J. 1998. Neuromodulatory inputs maintain expression of a lobster motor pattern-generating network in a modulation-dependent state: evidence from long-term decentralization in vitro. *J. Neurosci*. 18:212–25
169. Thoby-Brisson M, Simmers J. 2000. Transition to endogenous bursting after long-term decentralization requires de novo transcription in a critical time window. *J. Neurophysiol*. 84:596–99
170. Thoby-Brisson M, Simmers J. 2002. Long-term neuromodulatory regulation of a motor pattern-generating network: maintenance of synaptic efficacy and oscillatory properties. *J. Neurophysiol*. 88:2942–53
171. LeMasson G, Marder E, Abbott LF. 1993. Activity-dependent regulation of conductances in model neurons. *Science* 259:1915–17
172. Liu Z, Golowasch J, Marder E, Abbott LF. 1998. A model neuron with activity-dependent conductances regulated by multiple calcium sensors. *J. Neurosci*. 18:2309–20
173. Turrigiano G, Abbott LF, Marder E. 1994. Activity-dependent changes in the intrinsic properties of cultured neurons. *Science* 264:974–77
174. Turrigiano GG, LeMasson G, Marder E. 1995. Selective regulation of current densities underlies spontaneous changes in the activity of cultured neurons. *J. Neurosci*. 15:3640–52

175. Baro DJ, Coniglio LM, Cole CL, Rodriguez HE, Lubell JK, et al. 1996. Lobster *shal*: comparison with *Drosophila shal* and native potassium currents in identified neurons. *J. Neurosci.* 16:1689–701
176. MacLean JN, Zhang Y, Johnson BR, Harris-Warrick RM. 2003. Activity-independent homeostasis in rhythmically active neurons. *Neuron* 37:109–20
177. MacLean JN, Zhang Y, Goeritz ML, Casey R, Oliva R, et al. 2005. Activity-independent coregulation of I_A and I_h in rhythmically active neurons. *J. Neurophysiol.* 94:3601–17
178. Zhang Y, Oliva R, Gisselmann G, Hatt H, Guckenheimer J, Harris-Warrick RM. 2003. Overexpression of a hyperpolarization-activated cation current (I_h) channel gene modifies the firing activity of identified motor neurons in a small neural network. *J. Neurosci.* 23:9059–67
179. Baro DJ, Ayali A, French L, Scholz NL, Labenia J, et al. 2000. Molecular underpinnings of motor pattern generation: differential targeting of *shal* and *shaker* in the pyloric motor system. *J. Neurosci.* 20:6619–30
180. Baro DJ, Cole CL, Harris-Warrick RM. 1996. RT-PCR analysis of *shaker*, *shab*, *shaw*, and *shal* gene expression in single neurons and glial cells. *Recept. Channels* 4:149–59
181. Baro DJ, Cole CL, Harris-Warrick RM. 1996. The lobster *shaw* gene: cloning, sequence analysis and comparison to fly *shaw*. *Gene* 170:267–70
182. Baro DJ, Cole CL, Zarrin AR, Hughes S, Harris-Warrick RM. 1994. *Shab* gene expression in identified neurons of the pyloric network in the lobster stomatogastric ganglion. *Recept. Channels* 2:193–205. Erratum. 1994. *Recept. Channels* 2(4):350
183. Baro DJ, Harris-Warrick RM. 1998. Differential expression and targeting of K^+ channel genes in the lobster pyloric central pattern generator. *Ann. N.Y. Acad. Sci.* 860:281–95
184. Baro DJ, Quinones L, Lanning CC, Harris-Warrick RM, Ruiz M. 2001. Alternate splicing of the *shal* gene and the origin of I_A diversity among neurons in a dynamic motor network. *Neuroscience* 106:419–32
185. Clark MC, Baro DJ. 2006. Molecular cloning and characterization of crustacean type-one dopamine receptors: D1αPan and D1βPan. *Comp. Biochem. Physiol. B* 143:294–301
186. Clark MC, Dever TE, Dever JJ, Xu P, Rehder V, et al. 2004. Arthropod 5-HT2 receptors: a neurohormonal receptor in decapod crustaceans that displays agonist independent activity resulting from an evolutionary alteration to the DRY motif. *J. Neurosci.* 24:3421–35
187. French LB, Lanning CC, Harris-Warrick RM. 2002. The localization of two voltage-gated calcium channels in the pyloric network of the lobster stomatogastric ganglion. *Neuroscience* 112:217–32
188. French LB, Lanning CC, Matly M, Harris-Warrick RM. 2004. Cellular localization of *Shab* and *Shaw* potassium channels in the lobster stomatogastric ganglion. *Neuroscience* 123:919–30
189. Herrick FH. 1909. Natural history of the American lobster. *Bull. U.S. Bur. Fish.* 29:plateXXXIIII
190. Marder E, Bucher D, Schulz DJ, Taylor AL. 2005. Invertebrate central pattern generation moves along. *Curr. Biol.* 15:R685–99
191. Krenz WD, Nguyen D, Perez-Acevedo NL, Selverston AI. 2000. Group I, II, and III mGluR compounds affect rhythm generation in the gastric circuit of the crustacean stomatogastric ganglion. *J. Neurophysiol.* 83:1188–201

Annual Review of Physiology
Volume 69, 2007

Contents

Frontispiece
Clay M. Armstrong xx

PERSPECTIVES, *David L. Garbers, Editor*

Life Among the Axons
Clay M. Armstrong 1

CARDIOVASCULAR PHYSIOLOGY, *Jeffrey Robbins, Section Editor*

Mitochondrial Ion Channels
Brian O'Rourke 19

Preconditioning: The Mitochondrial Connection
Elizabeth Murphy and Charles Steenbergen 51

CELL PHYSIOLOGY, *David E. Clapham, Section Editor*

Iron Homeostasis
Nancy C. Andrews and Paul J. Schmidt 69

Transporters as Channels
Louis J. DeFelice and Tapasree Goswami 87

ECOLOGICAL, EVOLUTIONARY, AND COMPARATIVE PHYSIOLOGY, *Martin E. Feder, Section Editor*

Hypoxia Tolerance in Mammals and Birds: From the Wilderness to the Clinic
Jan-Marino Ramirez, Lars P. Folkow, and Arnoldus S. Blix 113

Hypoxia Tolerance in Reptiles, Amphibians, and Fishes: Life with Variable Oxygen Availability
Philip E. Bickler and Leslie T. Buck 145

ENDOCRINOLOGY, *Kathryn B. Horwitz, Section Editor*

Integration of Rapid Signaling Events with Steroid Hormone Receptor Action in Breast and Prostate Cancer
Carol A. Lange, Daniel Gioeli, Stephen R. Hammes, and Paul C. Marker 171

Nuclear Receptor Structure: Implications for Function
David L. Bain, Aaron F. Heneghan, Keith D. Connaghan-Jones, and Michael T. Miura 201

GASTROINTESTINAL PHYSIOLOGY, *John Williams, Section Editor*

Regulation of Intestinal Cholesterol Absorption
David Q.-H. Wang 221

Why Does Pancreatic Overstimulation Cause Pancreatitis?
Ashok K. Saluja, Markus M. Lerch, Phoebe A. Phillips, and Vikas Dudeja 249

NEUROPHYSIOLOGY, *Richard Aldrich, Section Editor*

Timing and Computation in Inner Retinal Circuitry
Stephen A. Baccus 271

Understanding Circuit Dynamics Using the Stomatogastric Nervous System of Lobsters and Crabs
Eve Marder and Dirk Bucher 291

RENAL AND ELECTROLYTE PHYSIOLOGY, *Gerhard H. Giebisch, Section Editor*

Molecular Mechanisms of Renal Ammonia Transport
I. David Weiner and L. Lee Hamm 317

Phosphatonins and the Regulation of Phosphate Homeostasis
Theresa Berndt and Rajiv Kumar 341

Specificity and Regulation of Renal Sulfate Transporters
Daniel Markovich and Peter S. Aronson 361

RESPIRATORY PHYSIOLOGY, *Richard C. Boucher, Jr., Section Editor*

Overview of Structure and Function of Mammalian Cilia
Peter Satir and Søren Tvorup Christensen 377

Regulation of Mammalian Ciliary Beating
Matthias Salathe 401

Genetic Defects in Ciliary Structure and Function
Maimoona A. Zariwala, Michael R. Knowles, and Heymut Omran 423

SPECIAL TOPIC, β-ARRESTINS, *Robert J. Lefkowitz, Special Topic Editor*

Regulation of Receptor Trafficking by GRKs and Arrestins
Catherine A.C. Moore, Shawn K. Milano, and Jeffrey L. Benovic 451

β-Arrestins and Cell Signaling
Scott M. DeWire, Seungkirl Ahn, Robert J. Lefkowitz, and Sudha K. Shenoy 483

Physiological Roles of G Protein–Coupled Receptor Kinases and Arrestins
Richard T. Premont and Raul R. Gainetdinov 511

Stop That Cell! β-Arrestin-Dependent Chemotaxis: A Tale of Localized Actin Assembly and Receptor Desensitization
Kathryn A. DeFea 535

Regulation of Receptor Tyrosine Kinase Signaling by GRKs and β-Arrestins
Christopher J. Hupfeld and Jerrold M. Olefsky 561

Indexes

Cumulative Index of Contributing Authors, Volumes 65–69 579

Cumulative Index of Chapter Titles, Volumes 65–69 582

Errata

An online log of corrections to *Annual Review of Physiology* chapters (if any, 1997 to the present) may be found at http://physiol.annualreviews.org/errata.shtml