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Full-Wave Rectification from a Mixed Electrical-Chemical Synapse

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Electrical and chemical synapses usually reinforce one another, but the pyloric late–to–lateral pyloric (PL-to-LP) neuronal connections in lobster stomatogastric ganglia create an inverted U-shaped transfer function between the two neurons: regardless of whether the PL membrane voltage swings positive or negative, the postsynaptic LP voltage will go negative. When the presynaptic cell voltage goes negative, the effect on the LP voltage is due to electrical coupling. During positive presynaptic voltages, the strong contribution of graded chemical inhibition from the PL to the LP neuron overrides the positive electrical coupling to produce net negativity.

AT CERTAIN TYPES OF SYNAPSES, long-lasting presynaptic voltage changes create equally long-lasting postsynaptic voltage responses. Although electrical coupling is the most familiar example of this, chemical synapses are often capable of maintained release of neurotransmitter in response to long-lasting changes in presynaptic voltage. Neurons that do not spike must use such graded chemical synaptic transmission (*1*), but some spiking neurons use it in addition to spike-evoked transmitter release (*2–5*). Like spike-evoked chemical synaptic transmission, graded chemical synaptic transmission may be excitatory or inhibitory.

In the stomatogastric ganglion of the spiny lobster, *Panulirus interruptus,* many neurons use a mixture of graded and spike-evoked chemical synaptic transmission (*3–5*). Of the 30 identified neurons of which the stomatogastric ganglion is comprised, 14 are involved in the central pattern generation for the pyloric rhythm used in processing food from stomach to gut (*6*). There are no excitatory chemical synapses in this system (Fig. 1, A and B): only electrical coupling and chemical inhibition are utilized. In our experiments, we studied the transfer function between lateral pyloric (LP) and pyloric late (PL) neurons from lobster stomatogastric ganglia. We now describe a property that emerges from a combination of electrical coupling and strong inhibitory chemical transmission: an input-output function that is shaped like an inverted U (*7*), not unlike the input-output function of a full-wave rectifier (for example, $y = -k|x|$).

The maintained effect of this mixed synapse is most easily seen (Fig. 1C) when tetrodotoxin is added to the tissue bath to block neuronal spikes (*8*). When the PL neuron is hyperpolarized with intrasomatically injected current, a similar (though attenuated) hyperpolarizing waveform is recorded in the soma of the LP neuron. This is typical of electrical coupling (*9*), and with pure electrical coupling a depolarization of the presynaptic neuron normally causes a parallel postsynaptic depolarization. As shown in trace D of Fig. 1C, however, depolarizing the PL neuron also causes a postsynaptic hyperpolarization. Trace D is not as rectangular as trace H from the hyperpolarizing stimulus; instead it has the peak-plateau waveform that characterizes graded chemical inhibition in the stomatogastric ganglion (*3, 10, 11*).

Exploration of a wide range of presynaptic stimuli of both polarities showed that the resulting input-output curve is an inverted U shape (Fig. 1D). Only for positive voltage changes of less than 12 mV does the positive output expected from electrical coupling exceed the small (near-threshold) contribution of chemical inhibition, creating a small range of PL voltages that have little effect on LP voltages. Otherwise, the sign of the output is insensitive to the polarity of the input.

For graded chemical inhibition to cancel positive electrical coupling potentials requires a particularly strong graded connection. There are several PL cells that make connections to LP cells; generally only one (and sometimes none) forms an inhibitory connection sufficiently strong to overcome the electrical coupling, resulting in an input-output curve such as that shown in Fig. 1D. Weaker connections may result in graded inhibition exactly canceling electrical coupling for positive stimuli, resulting in a diode-like curve providing half-wave rather than full-wave rectification.

The synaptic transmission between a cell pair can be modulated by activating a synaptic input to the presynaptic cell. The LP neuron is presynaptic to, and strongly inhibits, pyloric dilator (PD) neurons. Polarization of the PL neuron affects transmission from LP to PD neurons (Fig. 2, A and B): either depolarization or hyperpolarization of the PL neuron reduces the LP-to-PD neuronal response. Polarizing the PL neuron alone has no effect on PD neurons (since the LP neuron does not inhibit the PD neuron at rest with tetrodotoxin in the bath).

Although the pyloric rhythm can be generated and coordinated without neuronal spikes, by means of graded transmission alone (*5*), it typically operates with a combination of spike-evoked and graded synaptic transmission (*4*); Fig. 2, C and D, demonstrates the power of the PL neurons in modulating the pyloric rhythm (in saline without tetrodotoxin in the bath to block spikes). Inhibitory postsynaptic potentials

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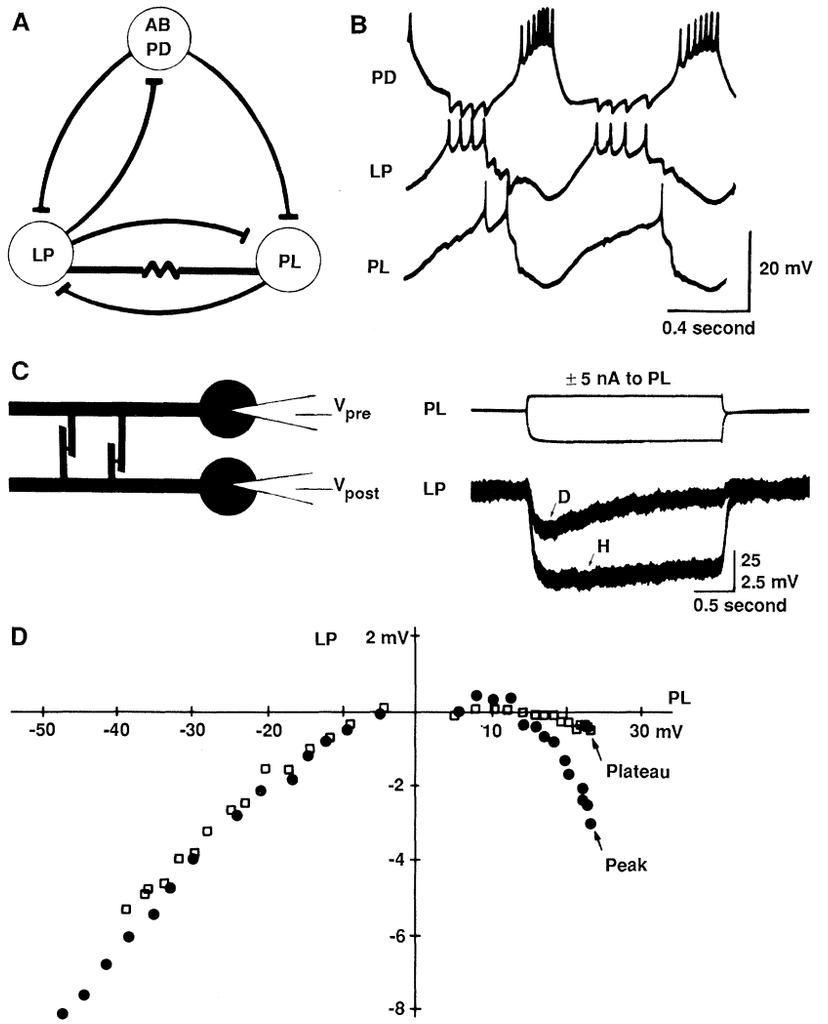

Fig. 1. (**A**) Schematic diagram of a portion of the pyloric circuit of the lobster stomatogastric ganglion, simplified to show the synaptic relations. The circles represent a single neuron or a group of electrically coupled neurons. The lines connecting the circles represent synaptic connections, the truncated line for chemical inhibition and the wavy line for electrical coupling. The simplified circuit includes the two pyloric dilator (PD) neurons, the anterior burster (AB) neuron, the lateral pyloric (LP) neuron, and the (approximately) three pyloric late (PL) neurons. (**B**) Normal oscillatory activity recorded in the cell bodies of neurons representing the three major cell types diagrammed in (A). Decremented spikes ride on large membrane potential oscillations. The amplitude and shape of spike-evoked inhibitory postsynaptic potentials vary with the cell pair. The data are from an isolated stomatogastric preparation after stimulation of the stomatogastric nerve to enhance activity. (**C**) Hyperpolarization with $4 \times 10^{-7} M$ tetrodotoxin in the bath. Both depolarizing (D) and hyperpolarizing (H) stimuli to the PL cell cause hyperpolarizing responses in the LP neuron. The stick figure shows that both electrical and chemical synapses are at a distance from the soma, on fine processes in the neuropil (*15*). V_{pre}, presynaptic potential; V_{post}, postsynaptic potential. (**D**) Input-output curve; $4 \times 10^{-7} M$ tetrodotoxin in the bath. Symbols: (●) peak pre- and postsynaptic responses; (□) the subsequent maintained plateau responses.

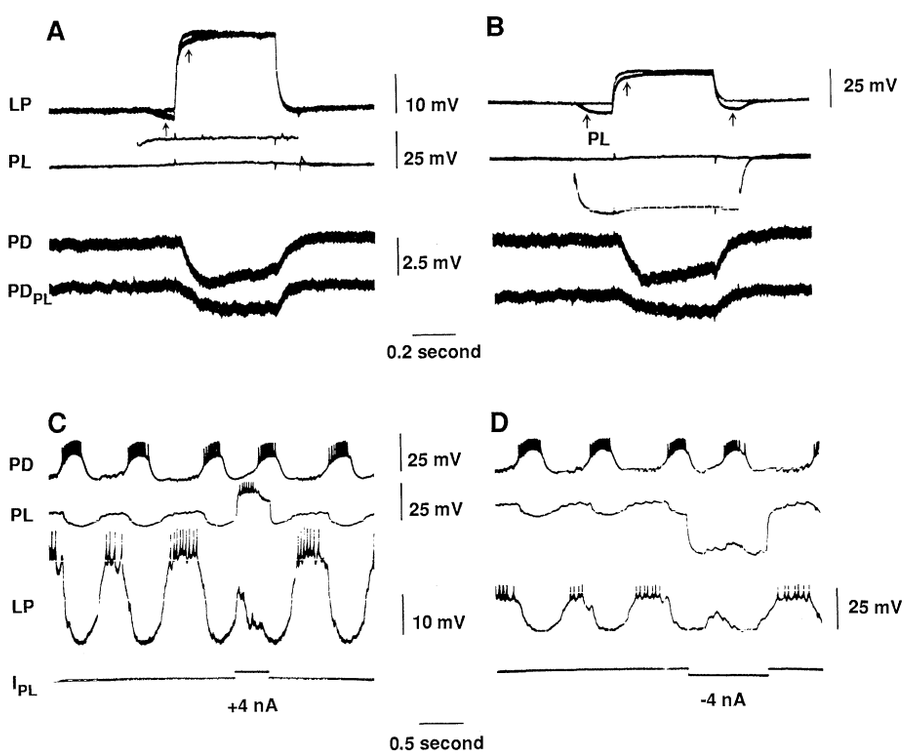

Fig. 2. Traces showing that depolarization and hyperpolarization of PL have the same circuit effects. (A) and (B) show presynaptic inhibition with $4 \times 10^{-7} M$ tetrodotoxin in the bath. Two trials are shown for (A) and (B), a control demonstrating the effect of depolarization of the LP neuron on PD potential with no PL stimulation (PD trace), and a second trial showing the effect of stimulating both PL and LP neurons (PD_{PL} trace and arrows in LP trace). The data for the two trials are superimposed for the LP and PL traces but are shown separately for PD traces. (**A**) Traces showing that depolarization of the PL neuron reduces PD inhibition by the LP neuron. (**B**) Traces showing that hyperpolarization of the PL neuron reduces LP-to-PD inhibition. In both (A) and (B), stimulation of the PL neuron alone has no effect on the PD potential. (C) and (D) show that, for spontaneous activity in a "combined preparation" with the commissural and esophageal inputs intact (*16*), PL stimulation resets the pyloric rhythm (normal saline in the bath). (**C**) Traces showing that depolarizing current into the PL neuron (bottom) causes depolarization and a burst of spikes in the PL neuron that inhibit the expected LP burst, thereby removing the normal LP inhibition of the PD neuron and allowing the next PD burst to advance. (**D**) Traces showing that hyperpolarization of the PL neuron produces the same effect on LP and hence on PD potentials.

can be seen in the PD trace from the spikes in the LP trace. When a brief depolarizing current is applied to the PL cell (Fig. 2C), the expected LP burst is inhibited, and the next PD burst occurs prematurely because of the absence of the usual inhibition. A similar response occurs if the PL neuron is hyperpolarized instead (Fig. 2D).

Thus during the typical pyloric pattern seen in active preparations, the PL neuron acts to help terminate the LP burst (Fig. 1B), allowing the PD neuron to fire sooner. The hyperpolarization of the PL neuron during the PD burst may also retard the LP depolarization and burst, thus modulating circuit activity during the hyperpolarizing part of the PL cycle when neurons are thought to be ineffective.

Finally, neuromodulators are known to modulate selectively the range of the normal voltage excursion and the firing patterns of these stomatogastric neurons (*12*). Such regulation should be capable of modifying the relative strengths of the mixed chemical-electrical synaptic connection, allowing one or the other effect to dominate. In other systems, modulators have been demonstrated to affect electrical coupling (*13*) and synaptic transmission (*14*), raising the possibility of even more marked shifts in the relative effectiveness of the electrical and chemical components of this mixed synapse. Thus this synaptic pair may be capable of switching its computations between full-wave rectification, half-wave rectification, and simple chemical inhibition or electrical coupling depending on modulatory input to this simple two-cell circuit and, by so doing, may modulate the patterned output of its larger neural network.

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8. Data are from six preparations, including both isolated stomatogastric ganglia and combined preparations (those with commissural and esophageal ganglia left attached). Data in Fig. 1B are from an isolated ganglion; Fig. 1, C and D, and Fig. 2 are from a combined preparation. Single- and double-barreled intracellular microelectrodes were used with either separate microelectrodes or separate barrels for injecting current and measuring voltage (*4*).
9. Hyperpolarization out for hyperpolarization in is also characteristic of a reduction in tonic chemically mediated excitation, which is not found in this network. Properties of electrical coupling and of mixed electrical-plus-excitatory chemical synaptic connections are reviewed by M. V. L. Bennett [in *Handbook of Physiology,* Section 1, *The Nervous System,* vol. 1, *Cellular Biology of Neurons,* J. M. Brookhart *et al.*, Eds. (American Physiological Society, Bethesda, MD, 1977), part 1, pp. 357–416.
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Technical Comments

Asymmetry of Neural Feedback in the Organization of Behavioral States

The nucleus locus coeruleus sends norepinephrine-containing projections to the entire cerebral cortex. Gary Aston-Jones *et al.* (*1*) show that this nucleus does not receive reciprocal projections back from the cortex. The overall connectivity pattern of this nucleus leads them to conclude that the widespread norepinephrine innervation of cortex is under a restricted set of afferent controls emanating mostly from a few medullary and hypothalamic nuclei.

We demonstrated this type of asymmetry in the connectivity of the nucleus basalis, which is the source of cholinergic projections for all cortical areas in the brain (*2*). Our studies in the rhesus monkey showed that the forebrain projections to this nucleus arise from a surprisingly restricted set of limbic and paralimbic regions. In contrast, the numerous sensory-motor and association areas of cortex which also receive cholinergic innervation send virtually no reciprocal projections back into the nucleus basalis. We concluded that the vast majority of the cortical surface has no direct feedback control over the cholinergic input that it receives, whereas a handful of limbic and paralimbic areas can exert monosynaptic control not only over the cholinergic input that they receive but also over the cholinergic projections that reach all other parts of the cerebral cortex. This pattern of connectivity implied that the nucleus basalis was poised to act as a cholinergic relay for modulating the activity of the entire cortical surface according to the prevailing motivational state encoded by the limbic and paralimbic regions of the brain.

Aston-Jones *et al.* show that the principle of asymmetrical neural control also holds for the nucleus locus coeruleus. An analogous arrangement is likely to exist in the connectivity of the brainstem raphe nuclei and of the substantia nigra–ventral tegmental area complex, which provide the cerebral cortex with serotonin and dopamine innervation, respectively. This pattern contrasts sharply with the great majority of corticocortical and corticothalamic connections that are reciprocal in a more symmetrical fashion.

The ascending corticopetal connections of the nucleus basalis, locus coeruleus, brainstem raphe, and substantia nigra are organized in such a way that a relatively small group of cells (under a restricted set of