Dopamine Modulates Graded and Spike-Evoked Synaptic Inhibition Independently at Single Synapses in Pyloric Network of Lobster

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Ayali, Amir, Bruce R. Johnson, and Ronald M. Harris-Warrick. Dopamine modulates graded and spike-evoked synaptic inhibition independently at single synapses in pyloric network of lobster. J. Neurophysiol. 79: 2063–2069, 1998. Bath application of dopamine (DA) modifies the rhythmic motor pattern generated by the pyloric network in the stomatogastric ganglion of the spiny lobster, Panulirus interruptus. Synaptic transmission between network members is an important target of DA action. All pyloric neurons employ both graded transmitter release and action-potential–mediated synaptic inhibition. DA was previously shown to alter the graded synaptic strength of every pyloric synapse. In this study, we compared DA’s effects on action-potential–mediated and graded synaptic inhibition at output synapses of the lateral pyloric (LP) neuron. At each synapse the postsynaptic cell tested was isolated from other descending and pyloric synaptic inputs. DA caused a reduction in the size of the LP spike-evoked inhibitory postsynaptic potentials (IPSPs) in the pyloric dilator (PD) neuron. The change in IPSP size was significantly and linearly correlated with DA-induced reduction in the input resistance of the postsynaptic PD neuron. In contrast, graded inhibition, tested in the same preparations after superfusing the stomatogastric ganglion (STG) with tetrodotoxin (TTX), was consistently enhanced by DA. DA shifted the amplitude of spike-evoked IPSPs in the same direction as the alteration of the postsynaptic cell input resistance at two additional synapses tested: DA weakened the LP spike-mediated inhibition of the ventricular dilator (VD) and reduced the VD input resistance, while strengthening the LP → pyloric constrictor (PY) synapse and increasing PY input resistance. As previously reported, graded inhibition was enhanced at these two LP output synapses. We conclude that DA can differentially modulate the spike-evoked and graded components of synapses between members of a central pattern generator network. At the synapses we studied, actions on the presynaptic cell predominate in the modulation of graded transmission, whereas effects on postsynaptic cells predominate in the regulation of spike-evoked IPSPs.

INTRODUCTION

Rhythmic motor patterns are generated by neural circuits called central pattern generators (CPGs) (Delcomyn 1980; Getting 1989; Marder and Calabrese 1996; Pearson 1993; Selverston and Moulins 1985). The motor pattern generated by a CPG depends on the intrinsic electrical properties of its component neurons and the synaptic interactions between the CPG members (Dean and Cruse 1995; Harris-Warrick 1993; Jacklet 1989; Rossignol and Dubuc 1994). The intrinsic neuronal properties and synaptic connectivity are, hence, important targets of neuromodulatory and sensory inputs, which modify an anatomically defined CPG to produce a wide variety of different motor patterns (reviewed in Grillner et al. 1994; Harris-Warrick 1994; Harris-Warrick and Marder 1991; Harris-Warrick et al. 1992; Marder et al. 1994).

We are studying the cellular and synaptic mechanisms by which dopamine (DA) modulates the 14-cell pyloric network of the stomatogastric ganglion (STG) of the spiny lobster, Panulirus interruptus. DA is an endogenous neuro-modulator in the stomatogastric nervous system of lobsters (Barker et al. 1979; Cournil et al. 1994; Kushner and Barker 1983; Kushner and Maynard 1977). It can sculpt a unique motor pattern from the pyloric neural network through its effects on particular ionic currents of the pyloric neurons (Eisen and Marder 1984; Flamm and Harris-Warrick 1986a,b; Harris-Warrick and Flamm 1987; Harris-Warrick et al. 1995a,b) and its distributed effects on synaptic strength between network neurons (Johnson and Harris-Warrick 1990, 1997; Johnson et al. 1993a,b, 1995).

All chemical synaptic transmission in the pyloric network is inhibitory (Fig. 1) and consists of two different components: 1) discrete spike-evoked inhibitory postsynaptic potentials (IPSPs) (Maynard 1972; Mulloney 1987) and 2) graded or chemotonic inhibition, where transmitter is released as a continuous function of voltage with a threshold at or even below the resting potential of the cell (Graubard 1978; Graubard et al. 1980, 1983; Maynard and Walton 1975). Graded synaptic transmission appears to be quantitatively most important for the organization of the pyloric motor pattern (Graubard et al. 1983; Hartline et al. 1988; Raper 1979). We have previously examined DA’s effects on all the graded chemical synapses within the pyloric network (Johnson and Harris-Warrick 1990; Johnson et al. 1993–1995). DA affects every graded synapse in the network in a variety of ways, strengthening some synapses while weakening others. DA has a complicated and sometimes opposing combination of pre- and postsynaptic actions to modify the net graded synaptic strength; at some synapses, for example, enhancements of graded release outweigh reductions in postsynaptic transmitter responsiveness to yield a net synaptic enhancement (Johnson and Harris-Warrick 1997).

We hypothesized that this differential modulation of the pre- and postsynaptic sites of a synapse by DA might lead to independent modulation of graded and action-potential–mediated synaptic transmission. To test this hypothesis, we examined DA’s effects on both spike-evoked and graded transmission at all the output synapses from the lateral pyloric (LP) neuron (Fig. 1). We concentrated on the LP → pyloric dilator (PD) synapses, where DA enhances graded transmission but reduces PD input resistance and responsiveness to the LP transmitter, glutamate (Glu) (Johnson et
al. 1995; Johnson and Harris-Warrick 1997). This synapse is of special interest because it serves as the only inhibitory input to the pyloric pacemaker group, composed of the two PD neurons electrically coupled to the anterior burster (AB) (Fig. 1) (Miller 1987; see also Manor et al. 1997). In addition, we looked at the LP → ventricular dilator (VD) and LP → pyloric constrictor (PY) synapses. DA enhances graded transmission at both of these synapses (Johnson et al. 1995) but weakens VD Glu responsiveness while strengthening PY Glu responsiveness (Johnson and Harris-Warrick 1997). Our results show that at these synapses, DA can modulate spike-evoked and graded transmission in opposite directions at a single synapse, and unlike graded transmission, modulation of action-potential–mediated transmission is primarily controlled by postsynaptic actions of DA on neuronal input resistance.

METHODS

Animals

Pacific spiny lobsters (P. interruptus) of both sexes weighing between 0.5 and 1.5 kg were purchased from Don and Lauree Tomlinson (San Diego, CA) and maintained in marine aquaria at 15–18°C until use.

Saline and chemicals

Panulirus saline was composed of (in mM) 479 NaCl, 12.8 KCl, 13.7 CaCl2, 3.9 NaSO4, 10 MgSO4, 2 glucose, 11.1 Tris base, and 5.1 maleic acid, pH 7.4–7.6 (Mulloney and Selverston 1974). All salts and drugs used for physiology were obtained from Sigma (St Louis, MO).

Physiology

The stomatogastric nervous system was dissected as described by Selverston et al. (1976) and placed in a preparation dish filled with Panulirus saline. The STG was desheathed, enclosed in a small (1 ml) pool of saline walled by petroleum jelly (Vaseline), and constantly superfused at 3 ml/min with oxygenated saline at 15–18°C. The cell bodies of the pyloric neurons were identified by correlation of action potentials recorded intracellularly in the soma and extracellularly on the identified motor nerve, and by the characteristic shape and timing of bursts of action potentials in the pyloric rhythm. Extracellular recordings were made from identified motor nerves using bipolar stainless steel pin electrodes. Standard intracellular techniques were used for two electrode current clamp in both pre- and postsynaptic cells. KCl-filled (3 M, 15–20 MΩ) microelectrodes were used for voltage recordings. For current injection we used KAc-filled (3 M + 0.25 M KCl, 20–25 MΩ) microelectrodes.

If not stated otherwise, inputs to the STG from higher ganglia were blocked after cell identification by applying 10−5 M tetrodotoxin (TTX) saline to a small pool walled with Vaseline on the desheathed stomatogastric nerve to stop rhythmic activity of the pyloric network (Nagy and Miller 1987; Russell 1979). For the three LP synapses studied (Fig. 1), the postsynaptic neuron was isolated by photoinactivation (Miller and Selverston 1979) of other cells chemically or electrically presynaptic to that cell (for LP → PD: AB, PD, VD; for LP → VD: AB, PDs; for LP → PY: AB, PDs, VD). However, complete isolation was not possible in all cases. For example, when testing a postsynaptic PY neuron, the other seven PY neurons were not photoinactivated. In addition, we cannot rule out some interactions between the pyloric neurons studied and terminals of descending inputs (Coleman et al. 1995; Nusbaum et al. 1992). The LP → PD synaptic transmission may be indirectly effected by DA through DA’s effect on the PD → LP cholinergic synapse. We believe such an effect to be very minor because we maintained both the LP and PD neurons at constant voltage by current injection. Hence there was no attempt to remove cholinergic inputs. The eight PY cells are known to be a heterogeneous group and can be split into two major subclasses (Hartline et al. 1987; Levini et al. 1994; Maynard 1972). We concentrated only on the PY1 or PL subclass that shows rectifying electrotonic coupling to the LP neuron (Fig. 1) and a general excitation in response to DA.

LP spikes were evoked by two methods. 1) We held the LP neuron very close to its spiking threshold (different in control and DA conditions) and allowed it to fire spontaneous single spikes; 2) we held the LP at a membrane potential of −80 to −85 mV and stimulated it with the shortest (15–20 ms) and smallest (varied) stimulus needed to generate a spike. Special care was taken to ensure that the brief stimulus generated no detectable graded inhibition, which tends to activate slowly following a current step. Preliminary experiments showed that the stimulus duration was shorter than the minimum necessary to generate graded inhibition. We monitored the stimulation of action potentials with an extracellular recording of the LP spike on the lateral ventricular nerve (lvn); in cases when the stimulus failed to generate a spike, no inhibition was ever seen. There was no difference between the inhibition evoked by spontaneous spikes or stimulation, when both methods were employed in the same preparation. The postsynaptic membrane potential was held between −55 and −45 mV, which differed between but not within experiments. Multiple IPSPs were recorded on videotape and later digitized (Axoscope software, Axon instruments) to allow superimposing and averaging of 10 single IPSPs in control and experimental conditions.

To determine the postsynaptic neuron’s input resistance, we injected the cell with 1 nA hyperpolarizing current pulses and averaged the voltage response for 10 repetitions.

In some preparations, after we examined spike-evoked inhibition at a particular synapse, we superfused the STG with 10−7 M TTX saline to block all spiking activity and then measured graded synaptic transmission at the same synapse. Graded inhibition was tested following the methods described by Johnson et al. (1995), with slight modifications. We held the presynaptic LP neuron at −55 mV and stepped it to −35 mV for 0.5 or 1 s to generate graded postsynaptic inhibition. Data were recorded and later digitized for analyzing and averaging results of five repetitions under control and experimental conditions.

DA saline solutions were prepared in normal and in TTX saline just before bath application at a final concentration of 10−4 M. The
postsynaptic response was tested before application, after 5 min superfusion and after ±30 min of washing.

RESULTS

Spike-evoked inhibition at the LP → PD synapse was clearly seen in an isolated LP-PD synaptic pair. As illustrated in Fig. 2A, the LP neuron action potentials (recorded distally on the lvn) as shown on the bottom extracellular trace, evoked discrete IPSPs in the postsynaptic PD neuron (top trace, Control). Bath application of DA had a strong inhibitory effect on the spike-evoked synaptic inhibition, causing a marked reduction in the peak IPSP amplitude (Fig. 2A, DOPAMINE). This effect was completely reversed after 30 min wash with normal saline. In eight experiments, the spike-evoked IPSP at the LP → PD synapse was significantly reduced by 36% from control values (Table 1, P < 0.005).

After measuring DA’s effects on the LP → PD spike-evoked IPSP, we superfused the STG with TTX saline and then measured graded transmission in the same preparation. In contrast to its reduction of spike-evoked transmission, DA caused an enhancement of graded synaptic efficacy (Fig. 2B) (Johnson et al. 1993a). In the example shown in Fig. 2, spike-evoked inhibition was reduced by 50% from the control value, whereas DA enhanced graded inhibition by 125%. In eight experiments, DA enhanced graded transmission at the LP → PD synapse by 87% from control values (Table 1, P < 0.05). This confirms our earlier results (Johnson et al. 1995). These results demonstrate that DA can enhance graded transmission and simultaneously reduce spike-evoked transmission at the same LP → PD synapse.

Table 1 also shows measurements of the PD neuron input resistance under control and DA conditions. As previously reported (Johnson et al. 1993a), bath application of DA caused a highly significant reduction in the PD neuron input resistance. In our experiments, the PD input resistance declined by an average of 34% in the presence of DA, a value very similar to the 36% decrease in the spike-evoked LP → PD IPSP. This led to a hypothesis that DA’s reduction of the spike-evoked IPSP arises primarily from a reduction in postsynaptic PD input resistance. We extended these results to a larger scale analysis of spike-evoked inhibition at the LP → PD synapse (n = 17). A strong linear correlation between spike-evoked IPSP size and PD input resistance was obtained with measurements combined from both control and DA conditions (Fig. 3A, P < 0.0001, F test for significance of the regression). The linear regression remained highly significant when testing the control and DA experimental conditions separately (P < 0.0001 and P = 0.0005, for control and DA conditions, respectively, n = 17). In addition, a highly significant linear fit was obtained when we tested the relation between the percent change in IPSP size and the percent change in input resistance evoked by DA (Fig. 3B, P = 0.005, nonparametric Spearman correlation test). This relationship has a slope of 0.97, not significantly different from a 1:1 relationship between these parameters. This strong linear correlation between the DA-

### TABLE 1. Dopamine effects on the two modes of synaptic inhibition and the input resistance of the postsynaptic cell

<table>
<thead>
<tr>
<th></th>
<th>IPSP Size, mV</th>
<th>Input Resistance, MΩ</th>
<th>Graded Inhibition, mV</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>DA</td>
<td>Control</td>
<td>DA</td>
</tr>
<tr>
<td>PD</td>
<td>−1.46 ± 0.81</td>
<td>−0.94 ± 0.81</td>
<td>7.89 ± 2.47</td>
<td>5.21 ± 1.88</td>
</tr>
<tr>
<td>VD</td>
<td>−0.44 ± 0.14</td>
<td>−0.11 ± 0.08</td>
<td>11.54 ± 4.04</td>
<td>7.25 ± 2.63</td>
</tr>
<tr>
<td>PY</td>
<td>−0.03 ± 0.16</td>
<td>−0.40 ± 0.15</td>
<td>10.67 ± 5.12</td>
<td>15.50 ± 6.28</td>
</tr>
</tbody>
</table>

Values are means ± SD (P value, paired Student t-test); n is number of experiments. IPSP, inhibitory postsynaptic potential; DA, dopamine; PD, pyloric dilator; VD, ventricular dilator; PY, pyloric constrictor.
cause it was still apparent when the PD membrane potential was maintained at its control value by injecting depolarizing current (Fig. 4A).

In addition to the PD neuron, the LP neuron forms a chemical inhibitory synapse onto the VD neuron and a mixed chemical inhibitory/rectifying electrical synapse onto the PY neurons (Fig. 1). We measured the effects of DA on these synapses to further test the idea of differential modulation of graded and action-potential-mediated inhibition, and the idea that DA’s modulation of postsynaptic input resistance contributes to determining the spike-evoked IPSP amplitude. DA acts postsynaptically to reduce the VD neuron input resistance (Johnson et al. 1993a) and to increase the PY neuron input resistance (Harris-Warrick et al. 1995a). Based on our results at the LP→PD synapse, we thus expected DA to reduce spike-evoked inhibition at the LP→VD synapse but to enhance spike-evoked inhibition at the LP→PY synapse. Figure 5 shows that this was indeed the case. In this example, the effects of DA on the spike-evoked IPSPs at all three LP output synapses were recorded in the same preparation. As expected from Fig. 2A, DA reduced the LP→PD spike-evoked IPSP in the PD neuron. DA also reduced the LP→VD spike-evoked IPSP as predicted, and this accompanied a significant 37% reduction in the VD input resistance (Table 1). The change reversed completely after wash. The LP→VD IPSPs under control conditions were much smaller than the LP→PD IPSPs. Thus although the reduction was clearly significant (an average 75%, Table 1), detailed and accurate analysis of the relation between DA’s evoked reduction in IPSP size and input resistance as presented for the PD was not possible in the case of the VD.

FIG. 3. A: relation between the size of LP neuron spike-evoked IPSPs in the PD neuron and the PD neuron input resistance ($R_{in}$), control conditions: ●, during DA bath application. Simple linear regression calculated for the pooled data ($n = 34$, $Y = 0.24 \cdot X - 0.39$, $R^2 = 0.673$). The linear fit is highly significant ($P < 0.0001$, $F$ test for significance of regression) and also stays highly significant when calculated separately for each of the experimental conditions (control, $P < 0.0001$; DA, $P < 0.0005$). B: DA effect on the IPSP size shown as % change from control, plotted against DA effect on the PD neuron input resistance ($R_{in}$) shown again as % change from control. Solid line shows a highly significant linear fit ($P = 0.0052$, nonparametric Spearman rank test, $n = 17$, $Y = 0.97 \cdot X + 5.60$, $r^2 = 0.519$).

induced percentage changes in the two parameters supports our hypothesis that DA reduces LP→PD spike-evoked transmission primarily by reducing the input resistance of the postsynaptic cell.

DA also clearly reduced LP→PD spike-evoked synaptic inhibition in a naturally cycling pyloric rhythm, when descending inputs from higher ganglia to the STG were left intact (Eisen and Marder 1982). Action-potential-mediated inhibition was always present as discrete IPSPs in the PD neuron that correlated 1:1 with LP spikes (Fig. 4A, Control). As seen in Fig. 4, A and B, the LP spike-evoked IPSPs in the PD neuron were smaller during DA bath application to the active pyloric network. This effect fully reversed after a wash with normal saline. The reduction in IPSP size was not due to any change in the peak amplitude of the LP cell or the frequency of LP spikes. Nor was it due to a reduced driving force resulting from DA-induced hyperpolarization of the PD neuron (Flamm and Harris-Warrick 1986b), be-

FIG. 4. Effects of dopamine on the LP→PD neuron synapse in a naturally cycling pyloric preparation. A: simultaneous intracellular recordings from the PD and the LP neurons under control conditions and in 10−4 M DA. The PD and LP trough membrane potentials were held at −50 in control and in DA by current injection. B: boxed areas of the PD traces in A are magnified to allow better comparison of control and DA conditions.
electrical coupling was seen. This gave way to a strong IPSP was often silent under control conditions, and only the electrotonic EPSP was seen in control. However, in respect to DA modulation of graded synaptic transmission at the LP neuron synapses. Our data strongly suggest that DA’s modulation of spike-evoked transmission at the LP synapses is primarily due to postsynaptic actions of the amine. We have previously measured DA’s effects on pyro- tonic coupling between the LP and the PD and VD neurons in control conditions (see text).

**DISCUSSION**

Our results show that DA can modulate the strength of spike-evoked synaptic transmission independently of its modulation of graded transmission at the same synapse. In two of the three synapses tested (LP → PD and LP → VD), DA’s modulatory effects on the two modes of inhibition were in opposite directions. In the third synapse tested (LP → PY), both graded and spike-evoked inhibition were enhanced, suggesting a synapse-specific, distributed modulation of spike-mediated inhibition (Table 1, Fig. 5).

Our results allow us to generate hypotheses about the possible sites of action for DA’S differential effects on spike- evoked and graded transmission. In theory, a modulator can act directly at the synapse, modifying either presynaptic transmitter release or postsynaptic transmitter receptor responsiveness. In addition, the modulator can act indirectly by modifying the pre- or postsynaptic neuronal input resistance, thus affecting current flow to and from the synapse. Table 2 summarizes our current knowledge of the modulatory effects of DA on parameters affecting synaptic transmission at the LP neuron synapses. Our data strongly suggest that DA’s modulation of spike-evoked transmission at the LP synapses is primarily due to postsynaptic actions of the amine. We have previously measured DA’s effects on pyro- tonic neuron response to iontophoretic application of the LP neurotransmitter, Glu (Johnson and Harris-Warrick 1997) (Table 2). Consistent with its effects on spike-mediated inhibition, DA reduced Glu responses in the PD and VD neurons and enhanced the PY neuron response. Our present data suggest that these changes in postsynaptic responsiveness arise at least in part from indirect effects on the postsynaptic neuron input resistance: DA reduces PD and VD input resistance but increases the PY input resistance (Tables 1 and 2). For the LP → PD synapse, we demonstrated a strong linear correlation, with a slope near 1, between DA’s percent modulation of input resistance and of spike-evoked IPSP amplitude. However, we cannot rule out an additional direct action of DA on postsynaptic Glu receptor responsiveness at the PD and VD synapses. Cleland and Selverston (1997) demonstrated that DA can reduce Glu receptor currents in unidentified, isolated, cultured STG neurons, and it is possible that the PD and VD neurons share this response. With respect to DA modulation of graded synaptic transmission at the LP → PD and LP → VD synapses, Johnson and Harris-Warrick (1997) concluded that DA acts presynaptically to sufficiently enhance LP transmitter release to outweigh a simultaneous reduction of postsynaptic Glu responsiveness. DA excites the LP neuron and causes a 28% increase in the cell’s input resistance (Harris-Warrick et al. 1995b). These effects could mediate in part the enhanced release from LP terminals. At the LP → PY synapse, both pre- and postsynaptic actions of DA would enhance the graded synaptic strength.

**TABLE 2. Summary of DA modulatory effects on synaptic transmission in the LP output synapses, as well as transmitter responsiveness and input resistance of the postsynaptic cell**

<table>
<thead>
<tr>
<th>Postsynaptic Cell</th>
<th>Graded Inhibition</th>
<th>Input Resistance</th>
<th>Glu Response*</th>
<th>Spike-Evoked IPSP</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD</td>
<td>↑</td>
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<tr>
<td>VD</td>
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<td>↓</td>
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<tr>
<td>PY</td>
<td>↑</td>
<td>↑</td>
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LP, lateral pyloric; Glu, glutamate. * From Johnson and Harris-Warrick (1997).
It is not clear how DA could enhance transmitter release for graded but not for spike-evoked transmission. In the network controlling heartbeat in the leech (see review by Calabrese 1995), it was found that the graded component of synaptic inhibition is activated by low-threshold Ca\(^{2+}\) currents (Angstadt and Calabrese 1991), whereas high-threshold Ca\(^{2+}\) currents selectively trigger spike-evoked transmission (Jin Lu et al. 1997). We do not know whether a similar distinction occurs in the lobster pyloric network; if so, a specific enhancement of the low-threshold Ca\(^{2+}\) currents could underlie DA’s selective enhancement of the graded release while leaving spike-evoked release relatively unchanged.

The ionic mechanisms underlying DA modulation of post-synaptic input resistance have not been fully defined. DA modulation of the transient potassium current, \(I_\text{K}\), may play a role: we have shown that DA decreases \(I_\text{K}\) to excite the PY neurons (Harris-Warrick et al. 1995a,b) and increases \(I_\text{K}\) to inhibit the PD neurons (Kloppenburg et al. 1997; Levini et al. 1996). Consistent with a role for \(I_\text{K}\), in preliminary experiments (data not shown) we found that the DA-induced modulation of the LP → PD spike-evoked IPSP disappeared when the PD was held at very hyperpolarized potentials (−80), where \(I_\text{K}\) is not active. However, blockade of \(I_\text{K}\) with 4-aminopyridine did not abolish DA modulation of PY responses to iontophotically applied Glu (B. R. Johnson, unpublished data), suggesting that other currents are also involved.

Graded synaptic transmission is used in both invertebrate and vertebrate chemical synapses (Burrows 1985; Dowling and Ripp 1973; Granzow et al. 1985; Graubard et al. 1983; Hartline and Graubard 1992; Raper 1979; Siegler 1985). The relative roles of graded and action-potential-mediated transmission vary between systems where the two modes of synaptic transmission coexist. In the leech heartbeat network, it was found that graded transmission occurs primarily at the beginning of the inhibitory period, and that subsequent sustained inhibition is spike mediated (Calabrese 1995). It is generally accepted that graded synaptic transmission plays the primary role in shaping the pyloric rhythm of the lobster (Graubard et al. 1983; Hartline et al. 1988; Raper 1979). DA can activate a pyloric rhythm with fairly normal frequency and phasing even after action potentials have been abolished with TTX (Anderson and Barker 1981; Raper 1979). Manor et al. (1997) did not find a unique role for LP spikes in LP → PD synaptic inhibition, other than a contribution to the overall hyperpolarization of the inhibitory response. However, measurements of IPSP amplitude in the cell body, rather than in the neuropil where they are generated, might selectively underestimate the rapid spike-evoked IPSP relative to the slow graded inhibition. The relative role of the two modes of transmission may also vary with the state of the system. For example, low, but still physiologically meaningful, temperatures can enhance spike-evoked inhibition while significantly suppressing graded transmission, and the pyloric motor pattern can continue to be generated (Johnston et al. 1991). Thus the quantitative importance of spike-evoked versus graded inhibition in the pyloric rhythm is not known.

Synaptic modulation is one of two major mechanisms (the other being modulation of intrinsic firing properties) by which neuromodulators reconfigure neural networks that mediate simple rhythmic behaviors (Dickinson et al. 1990; Grillner et al. 1994; Marder and Calabrese 1996). Independent and differential modulation of graded versus spike-evoked inhibition might prove to be an important tool to allow subtle variations in pattern generator output, to add flexibility and plasticity to the animal’s behavior.

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