Neural modulation: **Following your own rhythm**

Eve Marder

Recent studies of an invertebrate neural circuit show how presynaptic inhibition can play a key role in the generation of oscillatory activity, and can allow the directly affected axon terminal to engage in rhythmic activity independently of the rest of the neuron.

Address: Volen Center and Biology Department, Brandeis University, Waltham, Massachusetts 02254, USA.

Current Biology 1996, Vol 6 No 2:119–121

In the orderly world of the platonic neuron [1], axons and dendrites know their places, and information transfer follows predictable paths. The messy world of biological reality, however, is usually more complex and fascinating than a textbook caricature. A particularly intriguing example of this is the way that some neurons project into multiple ganglia, where they can show independent spike-initiating zones [2] and where regions of the neurons may be locally modulated [3]. Recent work from Michael Nusbaum and colleagues [4–7] demonstrates that an axon terminal in the stomatogastric ganglion (STG) of the crab *Cancer borealis* can function as an independent element in a circuit, and that presynaptic inhibition can play an important role in the generation of rhythmic motor patterns. Furthermore, the terminals involved have recently been shown [5] to constitute a critical circuit element in the generation of the crab's gastric mill rhythm — alternating bursts of activity in the motor neurons that drive the rhythmic movements of the teeth (gastric mill) within the crab stomach that grind and chew food.

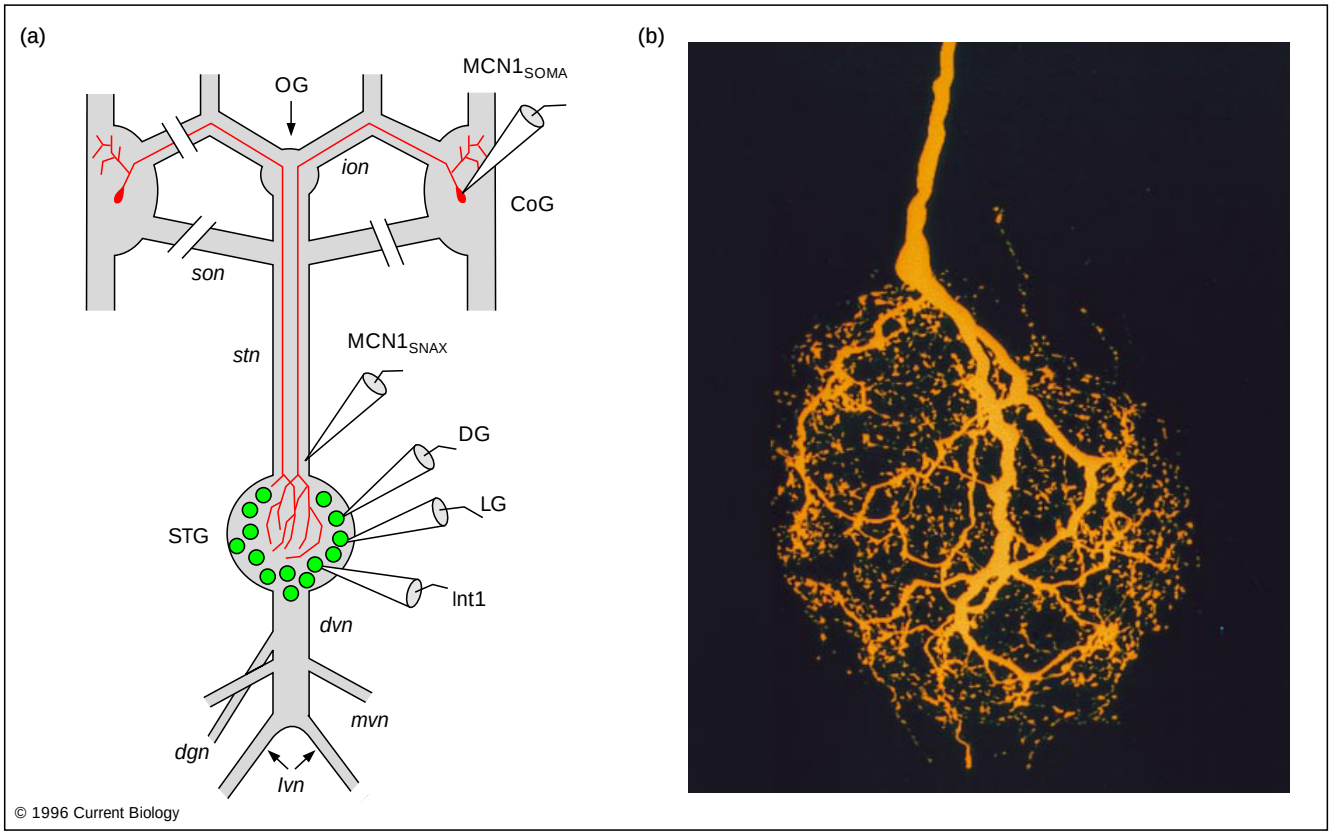
The new results of Coleman *et al.* [5] come from their studies of the functional importance of the connections between the terminals of the modulatory commissural neuron 1 (MCN1) and neurons in the crab STG. Nusbaum *et al.* [6] previously showed that it is possible to record intracellularly from stomatogastric nerve axons, such as that of the MCN1 (Fig. 1), and that this can be done close enough to their terminals to see discrete synaptic potentials elicted by neurons within their target, the STG. The recording configuration used by Coleman *et al.* [5] is illustrated in Figure 1a; and the axonal projection of the MCN1 neuron, just anterior to the STG, is shown in Figure 1b. Stimulation of the lateral gastric (LG) neuron of the gastric mill network in the STG was found to evoke an inhibitory postsynaptic potential (IPSP) in the MCN1 axon [6]. When the LG neuron fires in high frequency bursts, the MCN1 terminals are rhythmically inhibited during the bursts, although other regions of the MCN1 neuron maintain ongoing tonic activity [4,6].

MCN1 is an example of a modulatory neuron that can activate rhythmic pattern generation from a previously non-rhythmic circuit. Tonic stimulation of the MCN1 neuron activates the gastric mill rhythm, in which the dorsal gastric (DG) neuron, LG, and interneuron 1 (Int1) of the STG fire in rhythmic alternation. A model that can account for the alternating bursts of activity in these neurons is illustrated in Figure 2, and its key features are as follows. First, LG is electrically coupled to the MCN1 axon terminal. This electrical coupling is voltage-dependent, so that when LG is depolarized the electrical postsynaptic potential induced in MCN1 is larger than when LG is hyperpolarized. Second, LG inhibits the MCN1 terminal *via* a chemical synapse. Third, LG and Int1 reciprocally inhibit each other, and in principle form a classic 'half-center oscillator', in which network oscillations can occur because of reciprocal inhibition between two neurons that themselves fire tonically [8]. And fourth, MCN1 excites Int1 *via* a fast synapse, and excites LG and DG *via* a slow synapses. It is important that the excitatory postsynaptic potentials (EPSPs) evoked by the slow synapses depolarize their target neurons over several seconds.

The model can explain gastric rhythm production, as follows. When MCN1 is activated, it excites Int1 rapidly, and produces a slower excitation of DG and LG. When Int1 is strongly activated, it inhibits and hyperpolarizes LG, which reduces the strength of the electrical synapse between MCN1 and LG. LG stays off until it is depolarized enough by the slow EPSP from MCN1 to strengthen the effect of the voltage-dependent electrical synapse; the electrical and chemical synapses then combine to bring LG to threshold, allowing it to escape from Int1 inhibition and, in turn, to inhibit Int1. When LG starts to fire, it presynaptically inhibits transmitter release from the MCN1 terminals, leaving only the strong electrical synapse active. Why, then, does LG stop firing, so that the cycle can repeat? One important contributing factor is that the slow EPSP from MCN1, which helps activate LG, is terminated by LG's inhibition of the MCN1 terminal. As the influence of that slow EPSP wanes, LG starts to hyperpolarize, weakening the electrical synapse and presynaptic inhibition of MCN1, and the cycle repeats.

One of the fundamental problems in understanding oscillatory circuits is how synaptic strengths and time courses interact with the voltage-dependent currents intrinsic to

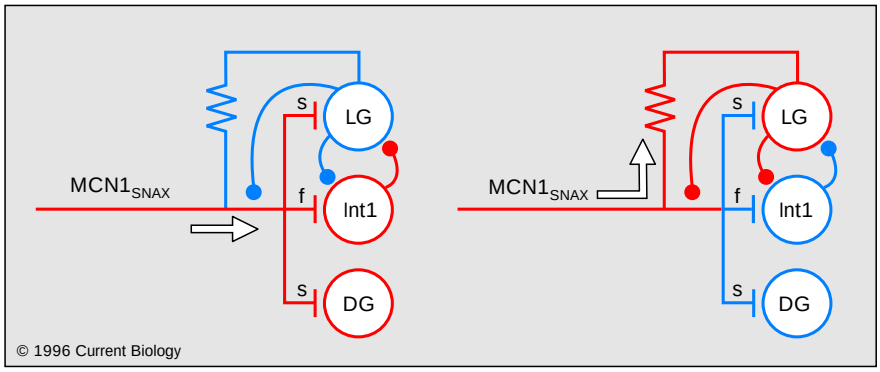
Figure 1



(a) Schematic diagram of the stomatogastric nervous system of the crab *Cancer borealis*, showing the position of the recordings made by Coleman *et al*. [5] and discussed in the text. CoG, commissural ganglion; OG, oesophageal ganglion; *son*, superior oesophageal nerve; *ion*, inferior oesophageal nerve; *stn*, stomatogastric nerve. (b) The axonal projection of $MCN1_{SNAX}$, filled with the fluorescent dye Lucifer yellow and imaged with a laser confocal microscope. (Image courtesy M.P. Nusbaum and A.E. Christie.)

each neuron in the circuit to determine the period of the oscillation [9]. The work of Coleman *et al.* [5] provides a plausible qualitative explanation of oscillation in the gastric mill circuit. However, the present work leaves unanswered the more quantitative questions of which processes are most important in determining the period of the oscillation, and how the period will change as synaptic strengths and intrinsic membrane properties are modulated. Answering these questions will require a combination of modelling and experimental work.

Figure 2



A model that can explain how presynaptic inhibition of the $MCN1_{SNAX}$ terminals could generate the gastric mill rhythm. Tonic activation of MCN, via stimulation of the inferior oesophageal nerve, activates the gastric rhythm,in which the STG neurons LG, Int1 and DG fire in rhythmic alternation. The diagram illustrates the mechanism underlying the transition between phases in which LG is inactive (left) and active (right). Active neurons (and synapses) are shown in red, and inactive neurons are shown in blue. Resistor symbol, electrical synapse; Filled circles, inhibitory synapses; flat bars, excitatory synapses (s,slow; f, fast). (Adapted from [5].)

The problem of understanding how the period of a circuit oscillator depends on the interaction of synaptic and intrinsic conductances has been more completely studied in the simpler case of a half-center oscillator formed from two virtually identical neurons coupled by reciprocal inhibition [8,9]. This circuit configuration is significant for the work of Coleman *et al.* [5], because the functional antagonists in the gastric mill circuit, Int1 and LG, also reciprocally inhibit each other. Classical half-center oscillations occur when the excitabilities of the two neurons and their synaptic connections are approximately balanced. In the absence of MCN1 activity, Int1 is strongly active and LG is silent. This argues that one important function of the MCN1 connections is to bring the LG excitability into the range where it balances that of Int1, so that the half-center oscillator formed by the two can operate. This then suggests that the period of the gastric mill oscillator may depend most directly on those factors that control the LG neuron's excitability, whether they be intrinsic to LG or the synaptic connections that it receives. Further experiments, together with theoretical work, on this mini-circuit will be instructive as we try to extend insights from simple half-center oscillators to more complex circuits with embedded half-center oscillators.

Presynaptic inhibition can give a nerve terminal a computational life that is independent of the activity patterns of the remainder of the neuron. In the case described by Coleman *et al.* [5], presynaptic inhibition is part of the circuitry that produces a network oscillation. Recent work on *Tritonia* [10] shows that a circuit element can have both conventional and modulatory effects. Similar combined functions are seen here: MCN1 can be called a modulatory neuron, in that its activation turns on a complete circuit, but its conventional synaptic connections are also part of the connectivity that is necessary for the circuit to operate. Presumably, as we learn more about modulatory control in nervous systems, we will discover more examples in which the distinction between modulatory neurons and the circuits that they modulate will be blurred. We now know that neurons that send projections to several spatially separate target areas may carry out separate computations in several local circuits, thus increasing the potential for significant behavioral flexibility.

Acknowledgements

Supported by NS17813, the Human Frontiers Science Program Organization and the W.M. Keck Foundation.

References

1. Adams P: The platonic neuron gets the hots. *Curr Biol* 1992, 2:625–627.
2. Vedel J-P, Moulins M: Functional properties of interganglionic motor neurons in the stomatogastric nervous system of the rock lobster. *J Comp Physiol A* 1977, 118:307–325.
3. Dickinson PS, Mecsas C, Hetling J, Terio K: The neuropeptide red pigment concentrating hormone affects rhythmic pattern generation at multiple sites. *J Neurophysiol* 1993, 69:1475–1483.
4. Coleman MJ, Nusbaum MP: Functional consequences of compartmentalization of synaptic input. *J Neurosci* 1994, 14:6544–6552.
5. Coleman MJ, Meyrand P, Nusbaum MP: A switch between two modes of synaptic transmission mediated by presynaptic inhibition. *Nature* 1995, 378:502–505.
6. Nusbaum MP, Weimann JM, Golowasch J, Marder E: Presynaptic control of modulatory fibers by their neural network targets. *J Neurosci* 1992, 12:2706–2724.
7. Nusbaum MP: Presynaptic control of neurones in pattern-generating networks. *Curr Opin Neur* 1994, 4:909–914.
8. Marder E, Abbott LF: Theory in motion. *Curr Opin Neur* 1995, in press.
9. Skinner FK, Kopell N, Marder E: Mechanisms for oscillation and frequency control in reciprocally inhibitory model neural networks. *J Computational Neurosci* 1994, 1:69–87.
10. Katz PS, Getting PA, Frost WN: Dynamic neuromodulation of synaptic strength intrinsic to a central pattern generator. *Nature* 1994, 367:729–731.