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The complexity of small circuits: the stomatogastric nervous system

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The crustacean stomatogastric nervous system is a long-standing test bed for studies of circuit dynamics and neuromodulation. We give a brief update on the most recent work on this system, with an emphasis on the broader implications for understanding neural circuits. In particular, we focus on new findings underlining that different levels of dynamics taking place at different time scales all interact in multiple ways. Dynamics due to synaptic and intrinsic neuronal properties, neuromodulation, and long-term gene expression-dependent regulation are not independent, but influence each other. Extensive research on the stomatogastric system shows that these dynamic interactions convey robustness to circuit operation, while facilitating the flexibility of producing multiple circuit outputs.

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Introduction

Studying neural circuits comes with a number of technical and conceptual challenges [1]. Any given circuit is not equally amenable to all technical approaches, which makes bridging levels of analysis difficult. In addition, numerical complexity, poorly defined cell types, and incomplete connectivity maps often make inferences from cellular to circuit function tentative at best. Furthermore, establishing functional boundaries for circuits embedded in larger brain areas can be difficult. Some of these problems are less severe in invertebrate preparations, which for this reason have been useful in unraveling evolutionarily conserved principles of circuit operation.

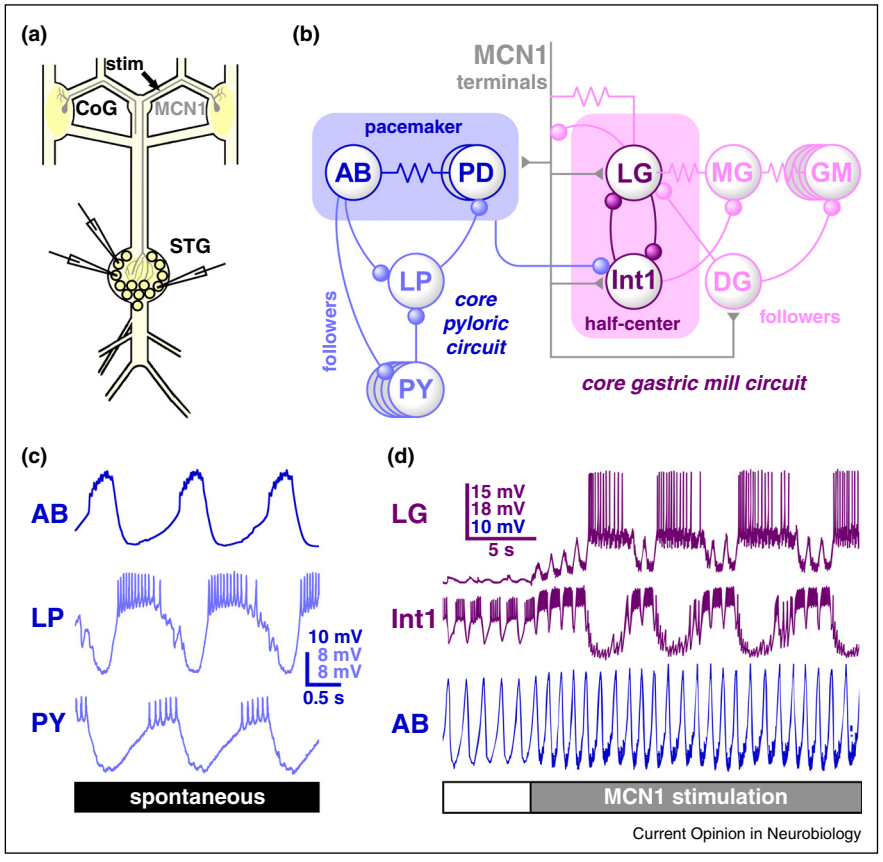
The stomatogastric nervous system (STNS) stands out for its utility in studying how neuronal and synaptic properties give rise to circuit activity and are shaped by neuromodulation and other regulatory processes [2]. The pattern-generating circuits of the STNS play an important role in feeding in all arthropods. However, the insect STNS has been studied mainly from a developmental and anatomical perspective [3], and although some of the activity patterns and neuromodulators involved in regulating feeding have been studied [4–6], the neural circuits that underlie these activities are as yet unidentified. Consequently, we will focus on the crustacean STNS.

In lobsters and crabs, the STNS is a conveniently anatomically separated system of a few ganglia that controls rhythmic activity of the foregut and can easily be studied *in vitro*. The stomatogastric ganglion (STG) contains only ~30 neurons, comprising two overlapping central pattern generating circuits that produce the slow gastric mill rhythm and the faster pyloric rhythm (Figure 1). The neurons are large and easily identifiable, and their connectivity has long been established. Considering the ongoing efforts in connectomics in many systems, it is humbling that such connectivity diagrams (Figure 1b) provide little explanation of circuit activity and dynamics. This is due to the nonlinear dynamics of membranes and synapses, neuromodulation, and long-term regulation, all of which can influence circuit activity over multiple time scales [7]. Here we review recent work on several aspects of these different time scales of circuit dynamics in the STG, and in particular how processes at different time scales interact.

Dynamics arising from intrinsic and synaptic properties

The pyloric rhythm is based on intrinsic oscillatory properties of a pacemaker kernel, and follower neurons burst in rebound from inhibition by the pacemaker [8] (Figure 1b,c). The gastric mill rhythm arises from synaptic connectivity of non-oscillatory neurons [9] (Figure 1b,d). The intrinsic neuronal and synaptic properties are well described in the STG, but it is not necessarily obvious how these components function within the context of circuit activity. Dynamics arising from the interactions of synaptic inputs and postsynaptic properties have recently been studied experimentally and theoretically in the context of how inhibitory feedback from follower neurons affects the pyloric pacemaker oscillation. At its usual timing with respect to the phase of oscillation, feedback inhibition has surprisingly little effect on the mean period of the rhythm, but reduces cycle-to-cycle variability and therefore stabilizes oscillations [10–12]. Similar stabilizing influences of

Figure 1



The pyloric and gastric mill central pattern generating circuits of the stomatogastric ganglion. **(a)** Schematic of the isolated STNS. The STG contains the pyloric and gastric mill circuits. The commissural ganglia (CoG) contain the cell bodies of projection neurons like the modulatory commissural neuron 1 (MCN1), which project to the neuropil of the STG. **(b)** The core pyloric and gastric mill circuit diagrams. Not all cells types and synapses are shown. Inhibitory chemical synapses are shown as circles, electrical coupling as resistor symbols, and excitatory inputs from MCN1 as triangles. Rhythm generation is based on intrinsic oscillatory properties of the pacemaker kernel in the pyloric circuit, and on reciprocal inhibitory connections between non-oscillatory neurons (half-center) in the gastric mill circuit. Note that both circuits are interconnected by direct synapses and through feedback to the terminals of projection neurons. **(c)** The typical tri-phasic pyloric pattern. In each cycle, a pacemaker burst is followed by neurons bursting in two different phases, in rebound from pacemaker inhibition. **(d)** The bi-phasic gastric mill rhythm is often not spontaneously active, but can be activated by stimulating modulatory projection neurons like MCN1. Note that the interconnection between both circuits leads to substantial pyloric modulation of the much slower gastric mill neuron bursting. The pyloric pacemaker neuron AB is shown as a reference for pyloric timing.
Source: (a, b, & d) are modified from Ref. [9]; (c) is modified from Ref. [8].

synaptic input on irregularly firing neurons have also been theoretically demonstrated for network-based oscillations [13]. The effect of timing of synaptic input with respect to the phase of ongoing activity also allows analyzing the contributions of specific ionic conductances [14]. Another window into how neuronal and synaptic properties shape circuit activity is provided by the observation that pyloric neurons and synapses have preferred frequencies, that is, show best responses at specific input frequencies. The distinct frequency preferences of different network components are correlated with the period of the rhythm and potentially the phasing of neurons, and are altered when neuromodulators change circuit activity [15•].

Neuromodulation

The STNS is perhaps best known for its role in uncovering principles of neuromodulation. Metabotropic actions of neuromodulators are at the root of the ability of circuits to produce different activity patterns [16–18]. The pyloric rhythm is continuously active and its stereotypical triphasic activity (Figure 1c) can be configured by neuromodulators *in vitro* into different temporal patterns. The gastric mill rhythm is often not spontaneously active, but can be activated by modulatory projection neurons to generate distinct patterns (Figure 1d). *In vivo* studies show that pyloric activity is indeed changed after feeding, and that distinct gastric mill rhythms exist in the intact