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Neural Circuit Flexibility in a Small Sensorimotor System

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Abstract

Neuronal circuits underlying rhythmic behaviors (central pattern generators: CPGs) can generate rhythmic motor output without sensory input. However, sensory input is pivotal for generating behaviorally relevant CPG output. Here we discuss recent work in the decapod crustacean stomatogastric nervous system (STNS) identifying cellular and synaptic mechanisms whereby sensory inputs select particular motor outputs from CPG circuits. This includes several examples in which sensory neurons regulate the impact of descending projection neurons on CPG circuits. This level of analysis is possible in the STNS due to the relatively unique access to identified circuit, projection, and sensory neurons. These studies are also revealing additional degrees of freedom in sensorimotor integration that underlie the extensive flexibility intrinsic to rhythmic motor systems.

Introduction

In the isolated CNS, central pattern generator (CPG) circuits produce fictive motor patterns that resemble the rhythmic motor patterns underlying behaviors in the intact animal [1][2][3][4][5][6]. However, the fictive pattern is generally not identical to the pattern in the behaving animal, partly due to the absence of sensory input in the isolated nervous system [7][8][9][10][11][12][13]. Sensory inputs often have phase-specific actions, but they can also have longer-term actions on rhythmic motor systems, including activating or terminating motor patterns and modulating ongoing motor activity [2][14][15][16][17][18]. Work in many systems, several of which are reviewed in this issue, continues to contribute to our understanding of sensorimotor integration. Here, we discuss recent work related to sensorimotor integration in the decapod crustacean stomatogastric nervous system (STNS), with an emphasis on how sensory inputs select particular motor patterns from multifunctional motor circuits.

The Stomatogastric System

The STNS has provided numerous insights into cellular, synaptic and circuit mechanisms by which rhythmic motor patterns are generated and modulated, due to its accessibility and the ability to manipulate identified neurons at multiple levels of the system [1][18][19]. Many of these insights clearly resonate with recent work in other systems, although often it remains challenging in other systems to obtain a similarly detailed level of analysis [20][21][22][23][24][25]. The STNS generates feeding-related rhythmic motor patterns, including those underlying chewing (gastric mill rhythm: cycle period ~10 s) and the filtering of chewed

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food (pyloric rhythm: cycle period ~1 s) within the multi-compartment foregut. Much of the work in this system focuses on the gastric mill and pyloric CPGs, which are located in the stomatogastric ganglion (STG) (Figure 1a) [1][18]. Projection neurons in the paired commissural ganglia (CoGs) innervate the STG and regulate its CPG circuits via electrical, ionotropic and metabotropic synaptic transmission [18][26] (Figure 1). These circuits are also modulated by a host of hormonal influences [1][18], and there are several identified sensory systems that provide mechanosensory information about muscle stretch, muscle tension or stretch of the stomach wall (Figure 1a) [16][18]. Collectively, these inputs enable the gastric mill and pyloric circuits to generate many gastric mill and pyloric motor patterns.

Sensorimotor Integration at the CPG- and Projection Neuron Level

In the STNS and other motor systems, sensory inputs act at multiple levels, including onto motor-, CPG- and projection neurons [1][2][14][16][27][28] (Figure 1b). One well-documented sensory feedback pathway in the crab STNS that acts on CPG and projection neurons is the muscle stretch-sensitive gastropyloric receptors (GPRs), which provide both cycle-by-cycle regulation and longer term modulation (Figure 1a). The GPR dendrites are embedded in gastric mill protractor muscles and, hence, they are activated during the gastric mill retraction phase (when protractor muscles are stretched) [29]. Their direct effects on the pyloric- and gastric mill CPGs include long-lasting modulation of the pyloric rhythm [30] [31] and a phase-specific action on the gastric mill rhythm [10][32••]. Additionally, as described below, GPR can activate the gastric mill rhythm via its excitation of identified projection neurons [33].

During gastric mill rhythms driven by the projection neuron MCN1, GPR selectively prolongs the gastric mill retractor phase [10][32••] (Figure 1c,2). This action might have been mediated by any or all of the GPR synapses on gastric mill CPG neurons (ionotropic excitation of Int1, metabotropic inhibition of LG and $MCN1_{STG}$: Figure 2b). Instead, it results entirely from GPR presynaptic inhibition of $MCN1_{STG}$, with the other two synapses being non-functional under this condition [10][32••]. Presumably these non-functional synapses come into play during other gastric mill rhythms (e.g. [34]). Interestingly, computational modeling and physiology manipulations indicate that GPR inhibition of $MCN1_{STG}$ is the only GPR action that selectively changes retraction duration during this gastric mill rhythm. When implemented experimentally, the other two GPR synapses instead alter both phases of this rhythm. These studies highlight (1) the ability of sensorimotor integration to involve synaptic regulation of projection neuron axon terminals, and (2) the possibility that sensorimotor integration can be modified under different conditions via changes in the relative strength of each sensory neuron synapse.

Sensorimotor integration can also involve the regulation of projection neuron activity. This is a pivotal locus, given the role of projection neurons in selecting distinct motor outputs from multifunctional neural circuits across species [2][26][35]. In some cases, the selection of overlapping but distinct sets of projection neurons determines motor output. This coding strategy is referred to as population coding [36][37]. This strategy is implemented to enable a muscle tendon organ receptor (AGR) and chemosensory input (via the IV projection neuron) to elicit distinct crab gastric mill motor patterns (Figure 1a) [38]. Interestingly, a population coding strategy also enables a single sensory neuron (AGR in lobster) to drive different motor patterns via distinct, activity-dependent synaptic actions onto two projection neurons [39]. Thus, sensorimotor integration can be adapted to the changing needs of an organism by both activity- and state-dependent regulation of sensory neuron synapses onto projection and circuit neurons.

In the STNS, more than one coding strategy underlies the selection of distinct gastric mill motor patterns [33][34][38][40]. In some instances, sensory pathways elicit distinct gastric mill motor patterns despite influencing the same projection neurons. For example, the GPRs and the mechanosensory ventral cardiac neurons (VCNs: see Figure 1a) each coactivate the projection neurons MCN1 and CPN2 but elicit different gastric mill motor patterns [33][41]. Another extrinsic input, the post-oesophageal commissure (POC) neurons, also activates MCN1 and CPN2 yet elicit a third distinct gastric mill motor pattern [40]. Therefore in addition to population coding, these studies illustrate that distinct motor patterns can be encoded at least partly within the activity patterns and firing rates of a conserved set of projection neurons [33][40][41].

Sensorimotor Gating

Sensory input is often locally regulated presynaptically, at sensory neuron axon terminals [28][42][43][44][45][46]. Thus far, however, in few cases has the downstream impact of these actions been elucidated at the cellular, synaptic and circuit levels. Recently, the impact of local gating of one sensory input by another sensory pathway at these multiple levels was determined in the lobster STNS [47••]. In this system, this gating action selectively down-regulates the sensory synapse onto one projection neuron, thereby switching the relative activity level of two projection neurons driven by the gated sensory input and altering the influence of that sensory input on the gastric mill motor pattern (Figure 3). Thus, interactions between sensory systems can occur presynaptic to their site of integration. Local gating of sensory feedback by a second sensory pathway in the crab STNS also switches the function of the gated pathway from an activator of projection neurons (and hence activator of the gastric mill rhythm) to a classical, phase-specific feedback pathway onto the CPG [10][33][40][41][48]. Another recently determined, novel consequence of sensorimotor gating is its ability to mediate behavioral choice, during feeding in the medicinal leech [49] (see Palmer and Kristan, this issue). Lastly, sensory input can also be “gated-in”. For instance, in the *Aplysia* feeding system, depolarization of the central soma and axon membrane potential rescues spike propagation and, with a distinct threshold, activates Ca^{2+} channels and therefore transmitter release [42][50][51•].

Sensory input is also commonly tuned for behavioral conditions, such as the hormonal state of the animal [52][53•]. For example, the GPR regulation of the MCN1-driven gastric mill rhythm is gated out by the peptide hormone CCAP (crustacean cardioactive peptide) [54••]. In normal saline, GPR selectively prolongs the gastric mill retractor phase, but this effect is eliminated when CCAP (threshold: $\leq 10^{-9}$ M) is present [52][54••][55] (Figure 2a, c). This occurs despite the CCAP direct actions on the gastric mill rhythm being a modest increase in the protractor phase and no change in the retractor phase duration. The CCAP gating action does not result from an influence on GPR, its synapse onto MCN1, or the MCN1 axon terminals [54••]. Instead, CCAP acts downstream of these sites by activating the same ionic current (I_{MI}) as MCN1 in a pivotal CPG neuron. Thus, when GPR weakens MCN1 peptide cotransmitter release [32••], CCAP-activated I_{MI} compensates for the reduced MCN1-activated I_{MI}, preventing the increased retraction duration (Figure 2c) [54••][55]. This study highlights the importance of evaluating the impact of modulation on motor output, even when it is apparently inconsequential, in the context of the larger sensorimotor system.

Peptide- and amine hormones also modulate muscle properties, neuromuscular transmission and sensory neuron responsiveness to muscle activity [56][57][58]. Recent work suggests a surprising hormonal role for GABA as well [59•][60]. For example, in the crab stomatogastric system, GABA was identified in the hemolymph and, in semi-intact preparations, found to strengthen both [glutamatergic] neuromuscular transmission and the resulting muscle contractions [59•]. Peripheral hormonal actions such as these will not only

alter the resulting muscle response, but the altered muscle contractions will likely modify proprioceptor feedback to the motor circuit.

State-dependent sensory actions can also result from changes in the timing of their activity. For example, during the crab gastric mill rhythm, the AGR neuron is activated by muscle tension and/or passive stretch [61][62]. In the former case, AGR is activated during the protraction phase and provides positive feedback that prolongs protraction, slowing the rhythm [63]. In the latter case, AGR is activated during retraction and provides negative feedback that shortens the protraction phase [63]. Phase-specific sensory actions, however, are not necessarily inverted when the feedback occurs during different phases of a motor pattern. In the crab STNS, for example, GPR selectively prolongs gastric mill retraction when activated during this phase [10], but when stimulated during protraction, GPR does not alter either gastric mill phase [32••]. Clearly, sensory input is highly dynamic and can change the information that it reports to central targets as well as the strength with which it acts on those central targets. Further, the sensitivity of central targets to this information is highly modifiable.

Sensory Neuron Specializations

Sensory neurons can have multiple spike initiation zones, as do other neuron types [28] [64] [65][66][67][68]. One such STNS sensory neuron is AGR, which generates spontaneous low frequency tonic activity at a central spike initiation zone, and fires phasically at a relatively high frequency from its peripheral processes in response to muscle stretch and tension [62] [63][69••] (Figure 4). Interestingly, the centrally-initiated AGR spikes influence motor output even without sensory transduction, indicating that “non-coding activity” of sensory neurons can adjust the “tone” of a rhythmic motor system [69••]. Put another way, AGR acts as an interneuron via its low-level tonic firing pattern and as a sensory neuron via its phasic responsiveness to muscle contraction or stretch (Figure 4). Additionally, only the centrally generated spike rate is modified by octopamine, highlighting the possibility for distinct regulation of the sensory and interneuron functions of this neuron [69••]. This study adds sensory neurons to the list of neuron types that are revealing the complexity of their axonal compartments, particularly regarding the presence of active properties that are subject to modulation [27][70][71][72][73][74][75][76].

Cotransmission

Cotransmission provides another level of complexity to sensorimotor integration, as to all aspects of neural signaling [26][45][77][78][79][80][81]. One well-studied multi-transmitter sensory neuron is GPR, which contains serotonin (5HT), acetylcholine (ACh) and allatostatin (AST) peptide [29][30][31][82]. GPR modulates the pyloric rhythm through distributed ionotropic and metabotropic actions on pyloric circuit neurons that involve at least 5HT and ACh [30][31]. In contrast, the phasic GPR regulation of the MCN1-driven gastric mill rhythm is mediated entirely by 5HT [32••] (Figure 2a, b). Thus, similar to projection and motor neurons [83][84][85], we now know that there can be divergence in the roles of sensory neuron cotransmitters.

Further extending the circuit flexibility afforded by cotransmission, the GPR (serotonergic) presynaptic inhibition of MCN1 affects the MCN1 slow, peptidergic excitation of the gastric mill protractor CPG neuron (LG) but not its fast, GABAergic excitation of the retractor CPG neuron (Int1) [32••][84] (Figure 2b). This study illustrates the very finely-tuned nature of sensorimotor integration. It also provides an example of how the same projection neuron can have state-dependent actions on its target circuit without requiring additional circuit modulation.

Parallel Sensory Feedback

Most cellular-level studies have examined the impact of a single sensory pathway at a time. However, in the intact animal, convergent sensory signals likely occurs regularly. Barriere et al. [47••] examined the convergent influence of two muscle sensory systems (AGR; posterior stomach receptors: PSRs) in the lobster STNS (Figure 3). Selectively stimulating AGR drives either of two gastric mill motor patterns, depending on the AGR firing rate [39]. The PSRs drive a single type of gastric mill motor pattern, which is also the one driven by a low AGR firing rate. These events result from AGR and PSR targeting the same two projection neurons (GI, CG), albeit via different synaptic actions (Figure 3). PSR ensures selection of a particular motor pattern by presynaptically inhibiting AGR and postsynaptically influencing GI and CG. Thus, to understand how sensory inputs select motor output one must not only determine their actions on CPG and projection neurons but also whether (and how) they interact with parallel sensory pathways. This system illustrates the additional complexity inherent in the intact sensorimotor system, as the AGR-elicited gastric mill motor pattern depends not only on the AGR firing rate and pattern (i.e. acting in its phasic, feedback mode or tonic, interneuron mode [69••]), but also on what parallel sensory pathways are influencing the same motor system (i.e. PSR neurons) [39][47••].

Conclusions/Future Directions

In vitro approaches have yielded considerable cellular-level information regarding the mechanisms underlying sensorimotor integration in rhythmic motor systems. The relatively unique access in the STNS to identified CPG, sensory and projection neurons and hormones has provided detailed cellular mechanisms, down to the level of independent regulation of cotransmitters and convergent actions on a single ionic current within a single neuron. Unexpected consequences for motor circuit output have come from examining parallel influences of hormonal and sensory inputs as well as multiple sensory inputs. However, given the complex interactions and the prevalence of feedback and feedforward loops in motor systems, yet more components will need to be included in the in vitro model systems to more fully mimic the complexities of the in vivo condition. Further development of in vivo approaches that enable closing such loops will also complement the in vitro approaches. For example, in vivo recordings from the crab STNS at multiple levels, including circuit and projection neurons [86•], show promise for extending our understanding of how an appropriate output is selected by sensory inputs acting in the complex background of the numerous modulatory, hormonal and sensory inputs that are likely to be co-active in the intact functioning animal.

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Highlights

- Neuronal circuits (CPGs) can generate rhythmic motor output without sensory input.
- Sensory input is pivotal for generating behaviorally relevant CPG output.
- We discuss cellular mechanisms whereby sensory inputs select different motor outputs.
- Sensory neurons can regulate the impact of projection neurons on CPG circuits.
- Degrees of freedom in sensorimotor integration enable flexibility in motor systems.

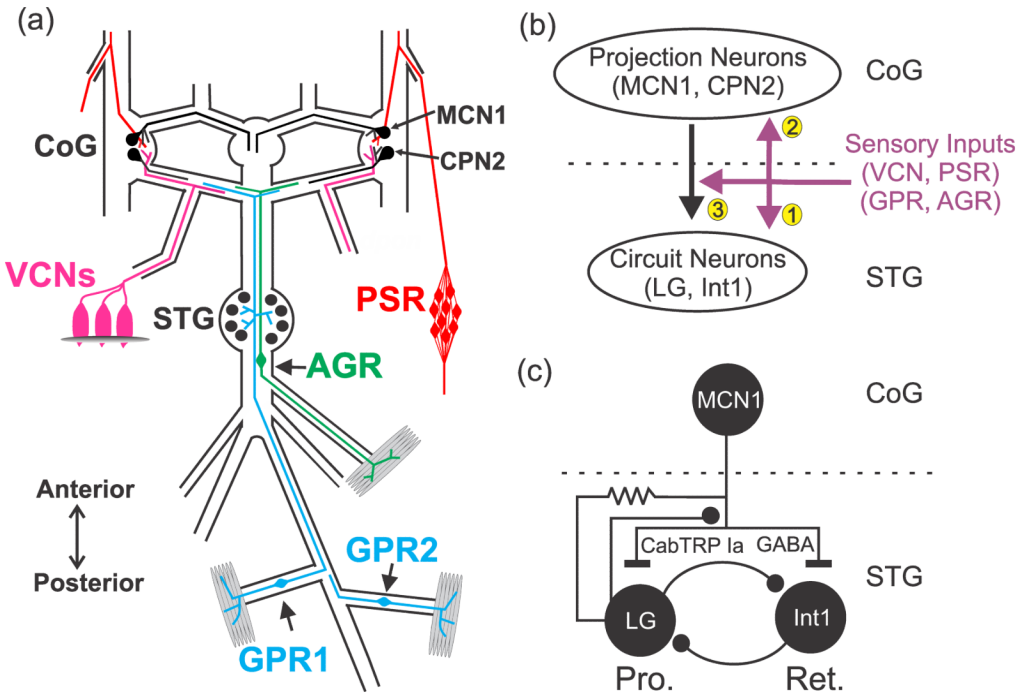

Figure 1.

Identified sensory and projection neurons in the stomatogastric nervous system. **(a)** Soma location and partial projection pathways of identified projection neurons (MCN1, CPN2) and sensory neurons (AGR, VCN, PSR, GPR1/2) are indicated. All projection and sensory neurons shown, except AGR, are bilaterally symmetric. For details, see [29][47••][61][87][88][89]. **(b)** Schematic illustration of the synaptic sites by which sensory inputs can select CPG output patterns, including via (1) actions onto CPG neurons, (2) actions onto projection neurons, and (3) presynaptic regulation of transmitter release from projection neurons onto CPG neurons. **(c)** The core CPG circuit diagram for the MCN1-driven gastric mill rhythm is shown. MCN1 uses its peptide cotransmitter CabTRP Ia to cause a slow excitation of the CPG neuron LG, and it uses GABA to cause a fast excitation of the CPG neuron Int1. LG inhibits transmitter release from the STG terminals of MCN1, without inhibiting its electrical coupling with MCN1. See references [84][90]. Symbols: filled circles, synaptic inhibition; t-bars, synaptic excitation; resistor, electrical coupling. Abbreviations: AGR: anterior gastric receptor; CabTRP Ia: *Cancer borealis* tachykinin-related peptide Ia; CoG: commissural ganglion; CPN2: commissural projection neuron 2; GABA: γ-amino butyric acid; GPR1/2: gastro-pyloric receptor 1/2; Int1: interneuron 1; LG: lateral gastric; MCN1: modulatory commissural neuron 1; Pro: protraction; PSR: posterior stomach receptors; Ret: retraction; STG: stomatogastric ganglion; VCN: ventral cardiac neuron.

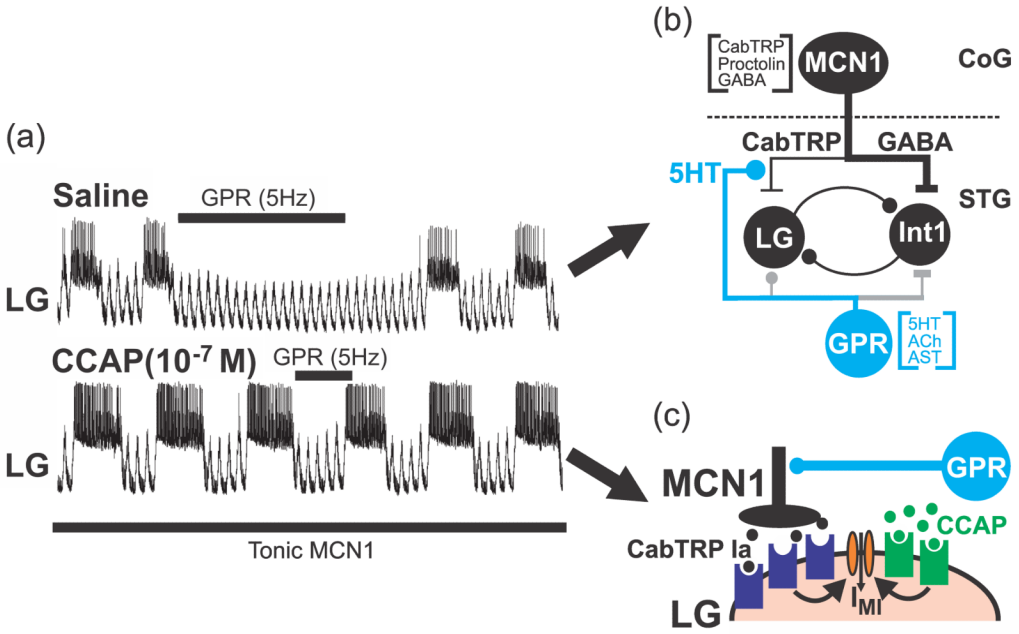

Figure 2.

Cotransmission and its modulation during sensorimotor integration in the crab STNS. **(a)** Tonic MCN1 stimulation drives the gastric mill rhythm, represented here by the regularly repeating bursting in the intracellular LG neuron recording. Top, During control conditions, GPR stimulation (during retraction phase: LG interburst) prolongs retraction, delaying the onset of the subsequent protraction phase (LG burst). Bottom, Bath applying the peptide hormone CCAP (10^{-7} M) weakens the GPR influence on the gastric mill rhythm. Adapted with permission from [54••]. **(b)** GPR prolongs the gastric mill retractor phase by using its cotransmitter 5HT to presynaptically inhibit the projection neuron MCN1. This action decreases the MCN1 release of its peptide cotransmitter CabTRP Ia (represented by the thinner MCN1 axon) without altering its release of GABA, thereby selectively weakening MCN1 excitation of LG. The GPR synapses onto LG and Int1 (grey) are not effective during the MCN1-driven gastric mill rhythm. Adapted with permission from [32••]. **(c)** The action of CCAP converges postsynaptically, in LG, with MCN1-released CabTRP Ia to activate the modulator-activated inward current (I_{MI}). This action enables CCAP to gate out the GPR action on the gastric mill rhythm by compensating for the decrease in CabTRP Ia-activated I_{MI} during the GPR presynaptic inhibition of MCN1. Adapted with permission from [54••]. Symbols as in Figure 1.

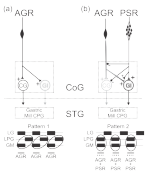

Figure 3.

Presynaptic regulation of parallel sensory feedback in the lobster STNS. **(a)** Moderate activity in the tendon organ receptor AGR excites the projection neurons CG and GI, with GI being less strongly activated than CG. The CG/GI co-activity elicits gastric mill motor pattern 1 (Pattern 1) from the gastric mill CPG in the STG. Pattern 1 is represented by the gastric mill motor neurons LG and GM generating co-active action potential bursts (filled black rectangles) that alternate with each LPG motor neuron burst. **(b**) Coactivating the muscle stretch-sensitive PSRs and AGR shifts the balance of projection neuron activity in favor of GI, via multiple mechanisms. First, the PSRs directly excite GI and inhibit CG. Second, they enhance GI activity by presynaptically strengthening AGR excitation of GI. Third, they reduce CG activity by presynaptically inhibiting the AGR excitation of CG. As a result, PSR/AGR coactivation drives a distinct gastric mill motor pattern (Pattern 2) in which LPG and GM bursts are coactive and alternate with each LG burst. Adapted with permission from [47••].

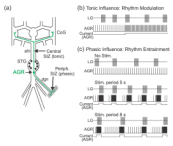

Figure 4.

Sensory and non-sensory functions of a tendon organ receptor in the crab STNS. **(a)** AGR has a peripheral spike initiation zone (SIZ), in or near its dendrites embedded in a gastric mill muscle, which generates phasic bursts of action potentials in response to rhythmic changes in muscle tension. AGR also has a central SIZ, located in the stomatogastric nerve (*stn*), which generates tonic spiking at a rate that is sensitive to locally applied octopamine [69••]. **(b)** Schematic showing that small changes in the tonic AGR firing rate generated by its central SIZ alter the cycle period of an ongoing gastric mill motor pattern (LG bursting). Adapted with permission from [69••]. **(c)** Schematic showing that phasic, higher frequency AGR spiking (mimicking its peripheral SIZ activation) entrains the gastric mill motor pattern (LG bursting). Adapted with permission from [61].