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Single neuron control over a complex motor program

(central pattern generator/mollusc/command neuron/*Tritonia*)

WILLIAM N. FROST* AND PAUL S. KATZ

Department of Neurobiology and Anatomy, The University of Texas Medical School, P.O. Box 20708, Houston, TX 77225

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ABSTRACT **While there are many instances of single neurons that can drive rhythmic stimulus-elicited motor programs, such neurons have seldom been found to be necessary for motor program function. In the isolated central nervous system of the marine mollusc *Tritonia diomedea*, brief stimulation (1 sec) of a peripheral nerve activates an interneuronal central pattern generator that produces the long-lasting (≈30–60 sec) motor program underlying the animal's rhythmic escape swim. Here, we identify a single interneuron, DRI (for dorsal ramp interneuron), that (*i*) conveys the sensory information from this stimulus to the swim central pattern generator, (*ii*) elicits the swim motor program when driven with intracellular stimulation, and (*iii*) blocks the depolarizing "ramp" input to the central pattern generator, and consequently the motor program itself, when hyperpolarized during the nerve stimulus. Because most of the sensory information appears to be funneled through this one neuron as it enters the pattern generator, DRI presents a striking example of single neuron control over a complex motor circuit.**

Over 30 yr ago, Wiersma and Ikeda (1) introduced the term "command neuron" to describe single interneurons in the crayfish that could drive coordinated movements of the animal's swimmerets. In its most restricted form, a command neuron is currently defined as a single interneuron, situated between sensory neurons and the motor pattern-generating circuitry, whose activity is both necessary and sufficient for sensory activation of the motor program (2). Many cells have now been described that can drive stimulus-elicited motor programs (3–13), but only rarely have such neurons been shown to also be necessary for circuit operation. Instead, in most cases these neurons have been found to operate in parallel with other circuit elements that fill-in when the cell in question is removed from the network (7–13). These and other findings have given rise in recent years to the view that, in most systems, command properties are distributed across broad interneuronal networks, with single neurons having only minor roles. We here describe a newly found interneuron in the *Tritonia* escape swim neural circuit that fulfills the strict definition of a command neuron (see also *Discussion*). The properties of this neuron, the dorsal ramp interneuron (DRI), provide further support for the original idea that the command function can be highly localized within a circuit, in this case, by funneling sensory information to the swim central pattern generator (CPG) and thereby controlling whether or not the swim motor program will be activated.

When the marine mollusc *Tritonia diomedea* encounters the tube feet of certain predatory sea stars, it responds with a vigorous rhythmic escape swim, consisting of a series of alternating ventral and dorsal whole-body flexions (14, 15). The neural circuit generating this behavior has been well-studied and consists of identified populations of afferent neurons (16, 17), CPG neurons (18–24), and efferent neurons (25, 26). The *Tritonia* swim CPG is a network oscillator; its rhythmic output (Fig. 1*C*) arises entirely from the synaptic connectivity of the neurons, with no cells having intrinsic bursting properties of their own (27). This network also operates with little or no need for sensory feedback and thus can be studied in isolated brain preparations (14).

A key missing element in the *Tritonia* swim network has been the hypothesized interneurons that transform the brief activity of the sensory neurons into the long-lasting, declining "ramp" depolarization in the dorsal swim interneurons (DSIs) of the CPG (28, 29). This depolarization serves as the main extrinsic excitatory drive for the swim motor program. Because of the strategic position of these neurons in the swim circuit, both in terms of their role in driving the motor program as well as their potential role as storage sites for learned information (30), we sought to locate them. We here identify a "ramp" interneuron in the *Tritonia* swim circuit, DRI, and find it to have an unusually prominent role for an individual neuron in the activation of a complex motor program.

MATERIALS AND METHODS

All experiments used an isolated central nervous system preparation, consisting of the left and right cerebral, pleural, and pedal ganglia. After removal from the animal the ganglia were pinned dorsal side up on the Sylgard floor of a recording chamber perfused with normal saline at 2°C. The connective tissue over the cerebral and pleural ganglia was then dissected away to expose the underlying neurons. Suction electrodes for extracellular recording and stimulation were made from polyethylene tubing and attached to the left and right pedal nerve 3 (PdN3), two of the many nerves that can be used to elicit the swim motor program (see Fig. 1*A* and ref. 25 for nomenclature). The preparation was then warmed to 10°C and rested for a minimum of 3 hr before beginning recordings. Swim motor programs were elicited with a brief stimulation of PdN3 (2-msec pulses, 10 Hz, 1 sec). This stimulus typically elicited a four to seven cycle swim motor program lasting 30–60 sec. Intracellular recordings were made with glass microelectrodes (10–40 MΩ) filled with either 3 M potassium chloride or 4 M potassium acetate. The CPG neurons were identified on the basis of soma location and coloration, synaptic interactions, and activity pattern during the swim motor program (20–23). DRI was labeled by iontophoretic injection of 5% carboxyfluorescein (Molecular Probes) in 0.1 M potassium acetate. Normal saline composition was as follows: 420 mM NaCl, 10 mM KCl, 10 mM $CaCl_2$, 50 mM $MgCl_2$, 10 mM Hepes (pH 7.6), and 11 mM D-glucose. High divalent-cation saline composition was as follows: 285 mM NaCl, 10 mM KCl, 25 mM $CaCl_2$, 125 mM $MgCl_2$, 10 mM Hepes, (pH 7.6), and 11 mM D-glucose. Animals were collected from Bellingham Bay, Washington.

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Abbreviations: CPG, central pattern generator; DRI, dorsal ramp interneuron; PdN3, pedal nerve 3; DSI, dorsal swim interneuron; EPSP, excitatory postsynaptic potential.

*To whom reprint requests should be addressed.

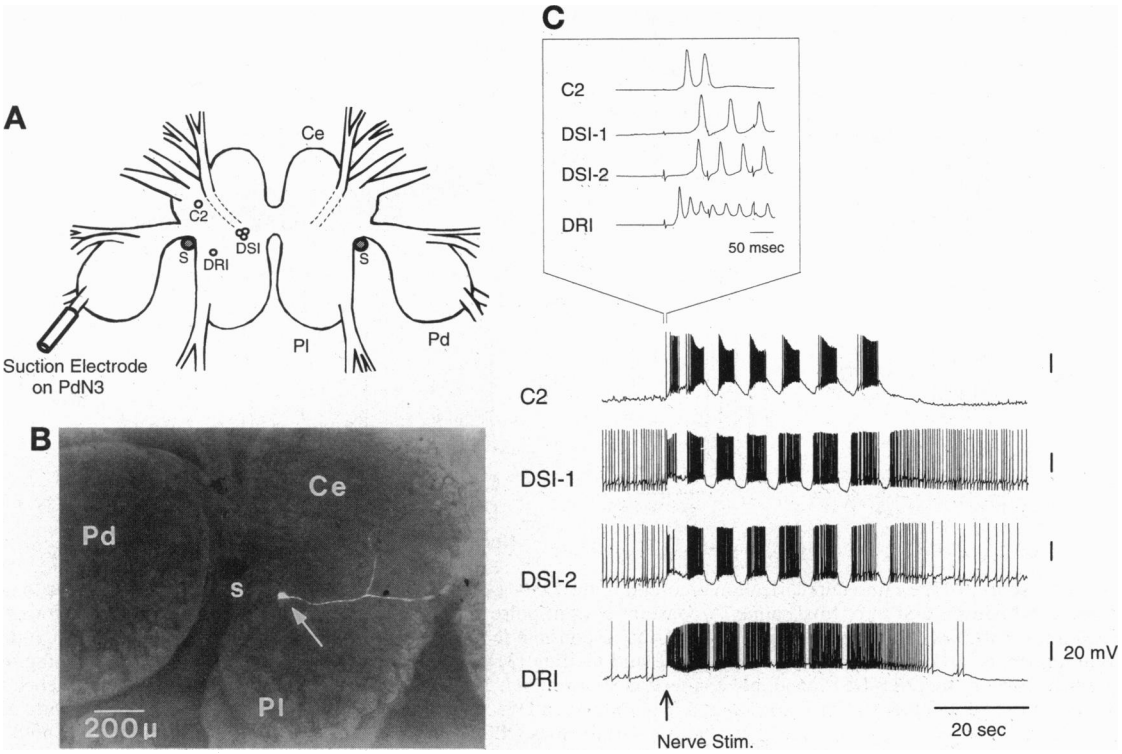

FIG. 1. Location, morphology, and firing behavior of DRI. (*A*) The soma of DRI is ≈20–30 μm in diameter and is located in the pleural ganglion, one or two cell body layers below the dorsal surface, medial and slightly caudal to the statocyst. All but two of our recordings were made from the DRI on the left side of the brain. (*B*) A photomicrograph showing a DRI (arrow) that was iontophoretically injected with carboxyfluorescein and illuminated with UV light. (A low level of transmitted light was used to visualize the rest of the tissue.) DRI has a major axon that travels toward the central commissure, which then gives off a minor branch extending rostrally near the region of the DSI somata. S, statocyst, Pd, pedal ganglion, Pl, pleural ganglion, Ce, cerebral ganglion. (*C*) Simultaneous intracellular recordings of DRI, two DSIs, and C2 during a swim motor program elicited by a 1-sec, 10-Hz stimulus to PdN3. The initial portion of the response to the nerve stimulus is expanded above and shows that DRI fired before the DSIs and C2. (Bars = 20 mV.)

RESULTS

This study began with an attempt to find "ramp" interneurons, previously hypothesized to provide the major excitatory input to the *Tritonia* swim CPG (28, 29). We were specifically looking for neurons that produced strong excitatory input to the DSIs and that could perhaps even drive the swim motor program when driven directly. After probing with a microelectrode in and around the central commissure, the axon of such a neuron was encountered. In two subsequent preparations, a similar axon was found in the same area and filled with carboxyfluorescein which, each time, labeled a cell body located in the dorsal pleural ganglion, near the statocyst (Fig. 1 *A* and *B*). Thereafter, recordings were made from the cell body itself. After further characterization, described below, the neuron was given the name "dorsal ramp interneuron" (DRI).

Brief stimulation of left PdN3 elicits the swim motor program in the isolated brain, during which the CPG neurons, cerebral cell 2 (C2) and the DSIs, fire in the dorsal phase of the oscillatory motor program (20). During the swim motor program, DRI fired in a more tonic fashion than C2 and the DSIs, with brief pauses during the ventral phase of the rhythm (Fig. 1*C*). Expansion of the initial part of the motor program revealed that DRI firing preceded the nerve-evoked activity in C2 and each of the DSIs (Fig. 1*C*), consistent with DRI having a position in the swim network afferent to the CPG.

In normal saline, DRI produced a large, constant latency, nondecrementing excitatory postsynaptic potential (EPSP) in each of the three DSIs on both sides of the brain ($n = 18$). This connection was strong enough to produce one-for-one firing in the DSIs at low DRI stimulation frequencies (0.1–2 Hz; data not shown) and significant spike activity in the DSIs at moderate-to-high DRI frequencies (3–30 Hz; Fig. 2*A1*). These EPSPs appeared to be monosynaptic because (*i*) they occurred one-for-one with DRI spikes, (*ii*) they began at a constant latency after the DRI spikes, (*iii*) they persisted in high-divalent cation saline (Fig. 2*A2*), and (*iv*) their amplitude was dependent on the DRI membrane potential (see refs. 21 and 32 for a discussion of these criteria). DRI made no direct connections to the other CPG neurons [C2, ventral swim interneuron A (VSI-A), or ventral swim interneuron B (VSI-B)] although it indirectly excited C2 via its powerful recruitment of the DSIs (data not shown).

The strong monosynaptic connection of DRI to the DSIs, together with its sustained firing throughout the swim motor program, suggested that it might contribute importantly to the ramp depolarization in the DSIs produced by PdN3 stimulation. To test this hypothesis directly, we examined the effect of silencing DRI on the DSI ramp input. In one preparation, we exposed the ramp depolarization in a DSI by hyperpolarizing it while simultaneously hyperpolarizing both C2s to prevent CPG oscillation (18, 19). A brief stimulus (1 sec, 10 Hz) was applied to PdN3, producing the ramp depolarization in the hyperpolarized DSI. This procedure was accompanied by a steadily declining firing response in DRI (Fig. 2*B1*). When we repeated this procedure with DRI also hyperpolarized, the ramp input to the DSI was substantially reduced (Fig. 2*B2*). This result suggests that DRI was responsible for the majority of the DSIs' extrinsic ramp input. We observed a similar loss of ramp input, as judged by the reduced firing response of the DSIs to PdN3 stimulation, in experiments in which DRI alone (and not the C2s) was hyperpolarized ($n = 4$—e.g., Fig. 3*B*). Given that PdN3 contains the axons of several dozen afferent neurons (17), DRI appears to serve as a restriction point for information flow in the *Tritonia* swim network—a funnel through which sensory information converges on its way to the CPG.

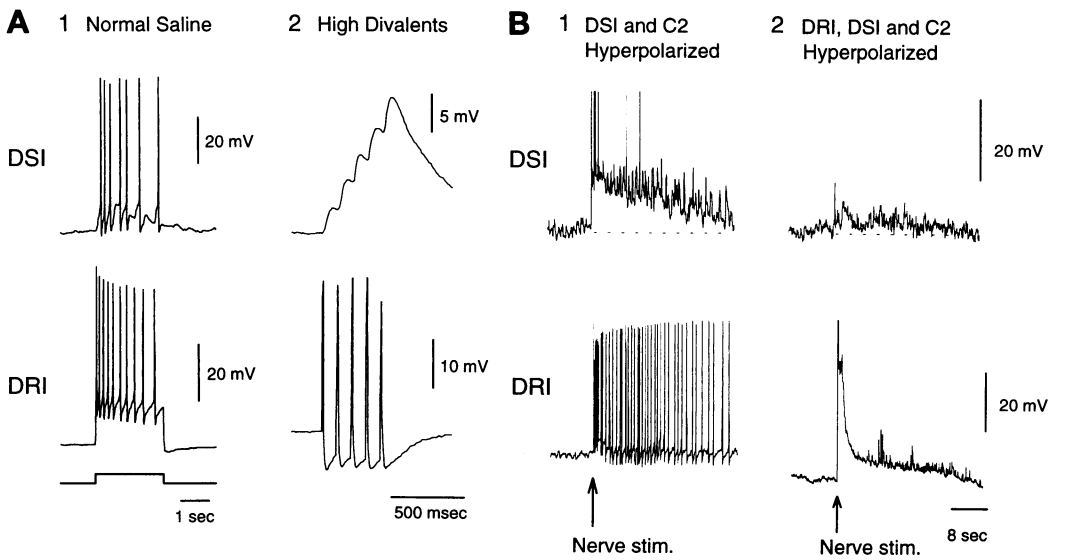

FIG. 2. DRI is the source of the ramp depolarization recorded in the DSIs. (*A*) Connection from DRI to a DSI. (*1*) The functional connection between DRI and CPG neuron DSI in normal saline. A constant current pulse (indicated by the stimulus marker below the trace) was injected into DRI to elicit a train of spikes, which produced a strong firing response in the DSI. (*2*) The same connection examined in high-divalent cation saline. This solution, similar to one previously used by Hume and Getting (31), raises all neuronal thresholds, thereby reducing or eliminating polysynaptic contributions to the DRI–DSI functional connection shown in *A1*. Brief intracellular current pulses were used to elicit five spikes in DRI, which produced five summating EPSPs recorded in a hyperpolarized DSI. (*B*) Effect of DRI hyperpolarization on the ramp depolarization in a DSI. (*1*) With both C2 neurons hyperpolarized (data not shown) to block CPG activity and a DSI hyperpolarized below threshold, a brief PdN3 stimulus produced prolonged firing in DRI and a ramp depolarization in the DSI. (*2*) Repeating the previous procedure, but with DRI hyperpolarized to prevent it from firing, largely abolished the ramp depolarization in the DSI.

Three additional observations further confirmed that DRI has a dominant role in this stimulus-elicited motor program. (*i*) Directly driving DRI at physiological rates elicited the swim motor program in every preparation in which it was examined (Fig. 3*A*, $n = 10$). During the nerve-stimulus-elicited swim motor program shown in Fig. 1*C*, DRI fired initially at 44 Hz, dropped rapidly to 16 Hz by 1 sec, and then stabilized at $\approx$7 Hz from 5 sec onward. By comparison, a constant depolarizing current pulse injected into the same DRI, which elicited the swim motor program shown in Fig. 3*A*, evoked a spike train that began at 28 Hz, rapidly declined to 18 Hz by 1 sec, and then stabilized at $\approx$9 Hz from 5 sec onward. In a separate protocol and preparation, driving DRI with discrete stimulator pulses at a fixed 10-Hz rate also elicited a swim motor program (data not shown).

(*ii*) The second observation confirming the dominant role of DRI in the swim motor program is that hyperpolarizing DRI, to block its sustained firing after the nerve stimulus, always prevented the swim motor program and greatly reduced the DSI firing response to the nerve stimulus (Fig. 3*B*, $n = 5$). This result demonstrates that DRI is necessary for eliciting the swim motor program via PdN3 stimulation. It is not yet known why hyperpolarizing one DRI blocks swim motor programs elicited by stimulation of either the left or right PdN3. We have recorded from a single DRI on each side of the brain. It could be that these two neurons are tightly electrically coupled and that hyperpolarizing one effectively suppresses activity in the other.

(*iii*) The third observation is that hyperpolarizing DRI during an ongoing swim motor program always quickly stopped the program (Fig. 3*C*, $n = 6$), indicating that continuous firing by DRI is necessary to sustain rhythmic motor activity.

Stimulus-elicited CPG circuits have commonly been found to produce feedback onto the interneuronal elements that drive them (4, 6, 33, 34). We have similarly observed that DRI receives feedback from the CPG, causing it to fire in phase with the rhythm (Fig. 1*C*). One source of this feedback appears to be inhibitory input in phase with the ventral portion of the rhythm. A second source of feedback to DRI is an indirect excitatory connection from the C2 neurons (Fig. 4). This synaptic potential appears to be indirect because (*i*) its amplitude was greatly reduced in high divalent saline, (*ii*) it had a variable latency, and (*iii*) it was not correlated one-for-one with C2 action potentials. Although polysynaptic, the C2 to DRI connection is frequently strong enough to activate DRI (Fig. 4*A*), and this DRI recruitment appears to be the primary source of the excitatory C2 to DSI connection previously described to occur in normal saline (21). When C2 failed to recruit DRI, either spontaneously (Fig. 4*B*) or because DRI was held hyperpolarized (data not shown), the strong excitatory effect of C2 on the DSIs disappeared.

DISCUSSION

These results identify DRI as an important neuron in the *Tritonia* escape swim neural circuit, with properties relevant to general issues of motor control. DRI is an example of a neuron that is capable of driving a stimulus-triggered, rhythmic motor program that satisfies the full set of criteria currently used to define a "command neuron." These criteria are as follows: (*i*) preferred access to sensory input, (*ii*) appropriate firing during the motor program, (*iii*) ability to drive the motor program directly when stimulated at physiological rates, and (*iv*) necessity of its firing for sensory input to be able to elicit the motor program (2, 13). Other examples of individual neurons that satisfy, or nearly satisfy, this full set of criteria include interneuron 1 in the cricket acoustic avoidance response (35), the lateral giant cell in the crayfish tail-flip response (36), and the Mauthner cell in the teleost fish and amphibian tail-flip responses (37). One difference between these examples and DRI is that in each of the other cases the neuron in question drives a brief, single-phase reflex response, quite unlike the rhythmic swim motor program considered here, which can last a full minute or more.

CPG neuron C2 has been previously referred to as a command neuron (19). However, it fails to satisfy all of the command cell criteria summarized above. For instance, it is only occasionally possible to elicit the swim motor program by

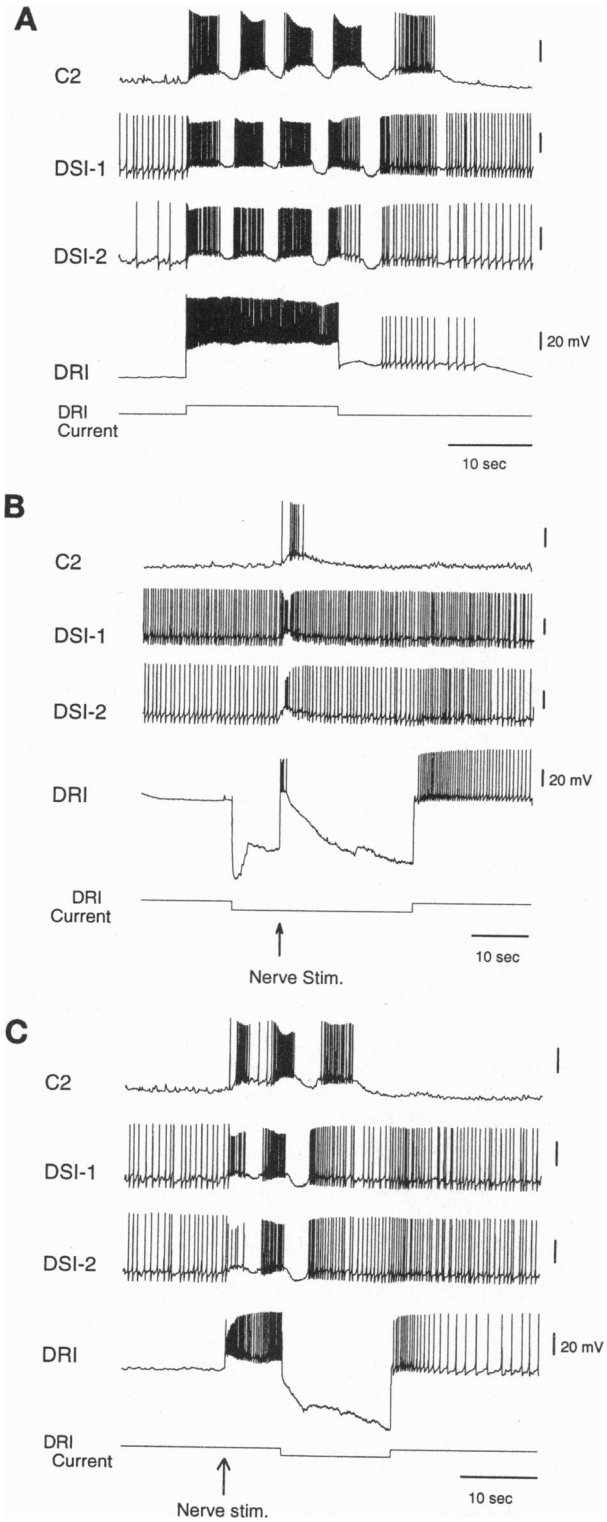

FIG. 3. DRI is necessary and sufficient for evoking the swim motor program. (*A*) Directly depolarizing DRI with intracellular current injection elicited the swim motor program. Simultaneous intracellular recordings of one C2 neuron, two DSIs, and DRI. (*B*) Hyperpolarization of DRI during a nerve stimulus prevented the triggering of the swim motor program and virtually eliminated the vigorous firing of the CPG neurons in response to the stimulus. An identical nerve stimulus delivered 2 min later elicited the six-cycle swim motor program shown in Fig. 1*C*. (*C*) Hyperpolarization of DRI during a swim motor program quickly halted the rhythm. Swim motor programs elicited 7 min earlier (Fig. 1*C*) and 8 min later (data not shown) without hyperpolarizing DRI were each six cycles in duration. Stimulus markers for the constant current pulses injected into the DRIs appear beneath each DRI trace.

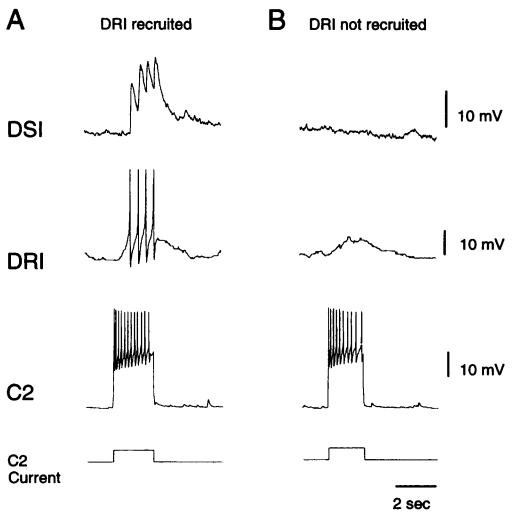

FIG. 4. In normal saline, C2 strongly excited the DSIs via recruitment of DRI. (*A*) C2 stimulation excited DRI, causing it to fire four spikes (shown clipped here). These in turn produced four fast, constant latency EPSPs in a DSI. (*B*) When an identical current pulse elicited two fewer spikes in C2, at a slightly lower frequency, C2 failed to recruit DRI, and the fast excitatory synaptic potentials in the DSI disappeared. Separate direct stimulation of the DRI evoked identical, constant latency fast EPSPs in the DSI (data not shown). Stimulus markers for the constant current pulses injected into C2 appear beneath each C2 trace.

directly stimulating C2 with intracellular current injection (18, 19). Furthermore, while C2 receives a fast monosynaptic EPSP from the sensory neurons, this input typically elicits just one or two action potentials in C2 at the onset of the swim motor program. Thus the majority of C2 input may be from other members of the CPG (29). On the basis of our present results, it seems likely that the occasional ability of C2 to elicit the swim motor program occurs via its recruitment of DRI.

Previous work showed that the postsynaptic targets of DRI, the DSIs, have two roles in the network: they make conventional synaptic connections onto several target neurons (21), and they also produce serotonergic heterosynaptic facilitation of C2 chemical synapses (38–40). Because DRI monosynaptically excites the DSIs, it directly activates this intrinsic modulatory system. By increasing the strength of C2 synapses, this neuromodulatory effect may enhance feedback from the CPG back onto DRI, effectively recruiting DRI into the pattern generator circuit. Additional work will be required to determine whether, during the swim motor program, DRI functions only as an upstream "driving" neuron or, due to its feedback, as a member of the CPG. If the latter, then the recruitment of DRI into the CPG would represent part of the mechanism by which this polymorphic network reconfigures itself from its resting nonoscillatory state into its rhythmic state (24). While DRI activity during the swim motor program is maintained, in part, by feedback from C2, blocking the CPG with combined DRI and C2 hyperpolarization reveals that DRI itself receives extrinsic excitatory input lasting several seconds (Fig. 2*B*). The source of this input has not been identified.

The data are, at present, most consistent with the existence of a single DRI on each side of the brain. Extensive searches have encountered no additional DRIs so far. Our findings that strong DRI hyperpolarization blocks nerve-elicited input to the DSIs (Figs. 2*B* and 3*B*), blocks the swim motor program itself (Fig. 3*B*), and brings an ongoing motor program to a rapid stop (Fig. 3*C*), support this interpretation. Furthermore, we always observed one-for-one correspondence between DRI spikes and fast EPSPs in the DSIs, whether driving DRI directly via current injection (Fig. 2*A*) or indirectly via C2

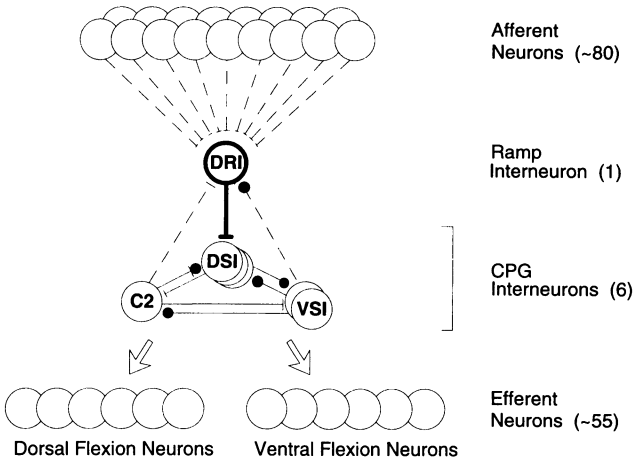

FIG. 5. A schematic of the functional *Tritonia* swim circuit, depicting the highly convergent route by which sensory information produces the ramp depolarization in the DSI neurons of the CPG. According to this scheme, DRI acts as a restriction point in the network, through which information must pass for the swim motor program to occur. Excitatory connections are depicted by bars, inhibitory connections by black dots, and dual component connections by combinations of symbols. Dotted lines indicate connections that are either polysynaptic or not yet known to be monosynaptic. The entire swim network contains >100 identified neurons on each side of the brain (23). The number of neurons in each class are indicated to the right of their labels. Each neuron has a contralateral homologue (not depicted).

stimulation (Fig. 4). In the latter case, this correspondence persisted when DRI activity was suppressed by relatively small hyperpolarizations (data not shown) or when C2 trains were used that were just below and just above threshold for recruitment of the single DRI recorded from (Fig. 4). In spite of these observations, the possibility remains, of course, that there are several DRIs on each side of the brain that receive input from PdN3 stimulation and that are all so tightly electrically coupled to one another that they always fire in complete unison. Further work, such as direct killing of DRI with photoinactivation or protease injection will be needed to decisively test this possibility. Such cell-kill experiments would also help test the possibility that other ramp interneurons convey input to the CPG from regions of the body surface innervated by nerves other than PdN3.

The simplest interpretation of our findings is that the *Tritonia* swim network has a highly restricted wiring scheme: sensory information arriving through PdN3 is funneled through an interneuronal bottleneck, where the firing of a single neuron appears to determine whether or not the motor program will occur (Fig. 5). The observations presented here contrast with an increasingly prevalent view that even simple behaviors are controlled by highly distributed neural networks (41–43). While the neural circuitry underlying behavioral responses may indeed be complex, our results support the idea, as envisioned many years ago (1), that the controlling elements of such circuits may themselves be strikingly simple.

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