Journal of Physiology - Paris 108 (2014) 148–154

Contents lists available at ScienceDirect

Journal of Physiology - Paris

journal homepage: www.elsevier.com/locate/jphysparis

Review paper

Recurrent inhibition in motor systems, a comparative analysis

Lidia Szczupak*

Departamento de Fisiología, Biología Molecular y Celular, FCEN-UBA and IFIBYNE UBA-CONICET, Pabellón II, piso 2, Ciudad Universitaria, Universidad de Buenos Aires, 1428 Buenos Aires, Argentina

ARTICLE INFO

Article history:
Available online 24 May 2014

Keywords:
Recurrent inhibition
Motor control
Nonspiking neuron
Electrical coupling
Leech

ABSTRACT

The review proposes a comparison between recurrent inhibition in motor systems of vertebrates and the leech nervous system, where a detailed cellular and functional analysis has been accomplished. A comparative study shows that recurrent inhibition is a conserved property in motor systems of phylogenetically distant species. Recurrent inhibition has been extensively characterized in the spinal cord of mammals, where Renshaw cells receive excitatory synaptic inputs from motoneurons (MNs) and, in turn, exert an inhibitory effect on the MNs. In the leech, a recurrent inhibitory circuit has been described, centered around a pair of nonspiking (NS) neurons. NS are linked to every excitatory MN through rectifying electrical junctions. And, in addition, the MNs are linked to the NS neurons through hyperpolarizing chemical synapses. Functional analysis of this leech circuit showed that heteronymous MNs in the leech are electrically coupled and this coupling is modulated by the membrane potential of NS neurons. Like Renshaw cells, the membrane potential of NS neurons oscillates in phase with rhythmic motor patterns. Functional analysis performed in the leech shows that NS influences the activity of MNs in the course of crawling suggesting that the recurrent inhibitory circuit modulates the motor performance.

Contents

1. Introduction

The generation of motor behaviors requires the control of a wide range of variables that ensures the coordinated activation of muscles across the entire body. Knowledge of the structure of motor systems in invertebrates and vertebrates has evolved noticeably in the past decades (Orlovsky et al., 1999; Graziano et al., 2002b; Grillner, 2003; Buschges et al., 2011), shaping new concepts within the classical model (Stein, 1978). The underlying networks are hierarchical in the sense that stimulation of neurons at the top can activate complex sets of movements (Brodfuehrer and Friesen, 1986; Edwards et al., 1999; Graziano et al., 2002a). Yet, at the bottom of the hierarchy, motoneurons (MNs) and premotor neurons form local networks that determine the spatial and temporal pattern of movement.

The concept of local circuits, distributed over invertebrate midbody ganglia (thoracic, abdominal, etc.) or vertebrate spinal cord, alludes to building blocks of motor behaviors, or "motor primitives" (Bizzi et al., 2000; Poppele, 2003; Buschges et al., 2008; Mulloney and Smarandache-Wellmann, 2012). Within each module the network commands characteristic patterns of activation of a particular set of muscles. These networks are composed

* Tel.: +54 1 145763368x110; fax: +54 1 145763321.
E-mail address: szczupak@retina.ar

http://dx.doi.org/10.1016/j.jphysparis.2014.05.004
0928-4257/

of excitatory and inhibitory connections between local interneurons and MNs.

This presentation focuses on the role of recurrent inhibition in motor systems (referred here as "motor recurrent inhibition") with the following plan: (i) a short review of recurrent inhibition; (ii) a description of a recurrent inhibitory circuit in the leech nervous system, where a detailed cellular and functional analysis has been accomplished; and (iii) a comparative analysis that will show that recurrent inhibition is a conserved property in motor systems of phylogenetically distant species.

2. Recurrent inhibition in motor systems

Almost every physiological function is subjected to negative feedback mechanisms that keep relevant variables within an optimal functional range (Cannon, 1929; Turrigiano, 1999; McCrea, 2001; Marder and Goaillard, 2006). Motor reflexes are classic examples of this general principle, where the outcome of MN activity is sensed in the muscle, and this sensory information is direct or indirectly fed back onto the MNs to adjust the contraction or elongation force (Burrows, 1992; Clarac et al., 2000; Hultborn, 2006). Motor networks are also provided with an additional feedback circuit, known as recurrent inhibition, that reads the MN signal at the time of its delivery to the muscle.

This type of feedback circuit has been extensively characterized in the spinal cord of mammals, where spinal Renshaw cells receive excitatory synaptic inputs from MNs and, in turn, exert an inhibitory effect on MNs (Renshaw, 1941; Eccles et al., 1954; Alvarez and Fyffe, 2007). Recurrent inhibition in the spinal cord is distributed between homonymous and heteronymous motoneuron groups (projecting to the same or different muscles, respectively); and any single Renshaw cell receives excitatory inputs from diverse motoneurons (Brink and Suzuki, 1987; Hamm, 1990). During rhythmic activity the membrane potential of Renshaw cells oscillates in phase with the pattern of motor activity (McCrea et al., 1980; Pratt and Jordan, 1987; Nishimaru et al., 2006). Different Renshaw cells fire during the flexor or extensor phase, indicating that during the rhythmic activity each interneuron is coupled with a functionally specific MN group. A major question regarding recurrent inhibition is what is the role of the information that is fed back to the central nervous system (Alvarez and Fyffe, 2007).

Recurrent inhibition can adopt different configurations in different organisms and in the leech nervous system this network function is mediated by electrical and chemical synapses centered around a nonspiking premotor neuron that forms a tight network with every excitatory motoneuron.

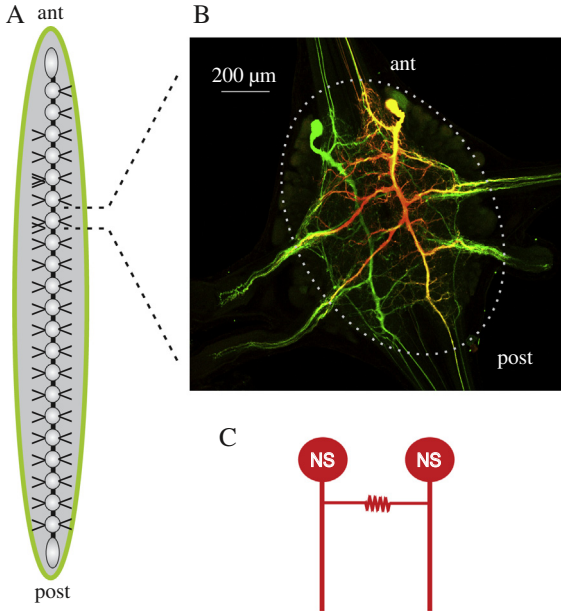

Fig. 1. Anatomy of NS neurons. (A) Scheme of *Hirudo* nervous system, composed of a chain of 21 midbody ganglia (represented by circles), flanked by a head and a tail brain (represented by ovals). (B) Confocal image of a ganglion (whose approximate outline is marked by dotted line) where one of the NS neurons was filled with a mixture of Rhodamine dextrane 3 K and Neurobiotin (revealed by Avidin bound to Fluorescein). The NS neuron injected with the dye mixture is revealed in yellow-orange, while the contralateral NS is revealed in green. (C) The pair of bilateral NS neurons is linked by ohmic electrical connections (Wadepuhl, 1989).

3. The recurrent inhibitory circuit in the leech

The nervous system of the leech has a simple general structure that reflects the relatively simple body plan of this annelid. The leech nervous system is composed of 21 midbody ganglia, aligned between a head and a tail brain (Fig. 1A) (Mann, 1962; Muller et al., 1981). Each midbody ganglion innervates one body segment, and thus the nervous system is indicative of a segmental anatomical organization where each segment, and correspondingly each ganglion, is highly similar to the others (the exceptions to this general pattern are segments 5 and 6 that contain the reproductive system).

This anatomical structure implies that, at first approximation, learning the network characteristics at the single ganglion level gives valuable information about the whole nervous system. To what extent is this notion true? Each ganglion contains the complete set of motoneurons that control the body wall muscles of the corresponding segment (Stuart, 1970); and of mechanosensory neurons (Nicholls and Baylor, 1968) that innervate the corresponding segmental skin; and a large variety of interneurons are iterated in each ganglion (Frank et al., 1975; Lockery et al., 1989). Thus, potentially, the single ganglion can operate with some autonomy.

In a segmented nervous system like that of the leech, the concept of local circuits, alluded to previously, is anatomically defined by the segmental ganglion that controls the movement of the corresponding segment. Networks contained within each ganglion underlie the different behaviors displayed by the animal (Kristan et al., 2005). The same MNs are used to swim and crawl under different spatio-temporal regimes of contraction and relaxation. Rhythmic motor patterns are primarily regulated by central pattern generators, whose components are iterated in each ganglion.

In this annelid a well-defined recurrent inhibitory circuit, centered around one bilateral pair of nonspiking (NS) neurons, has been described. The NS neurons are linked to all the excitatory MNs via rectifying junctions and MNs are connected to NS via inhibitory chemical synapses (Wadepuhl, 1989; Rela and Szczupak, 2003).

The somata of NS neurons are found in each midbody ganglion, at the anterior end of its ventral surface (Fig. 1B). Because of its location in the ganglion map the cell was initially identified as cell 151 (Wadepuhl, 1989), and was later named NS (Rela and Szczupak, 2003). This neuron is readily recognized because it does not fire Na^+-dependent action potentials (while all the other neurons in that region of the ganglion do) but it fires a low threshold Ca^{2+} spike on the rebound from a deep hyperpolarization (Rela and Szczupak, 2003; Rela et al., 2009). If filled with a chemical probe that is able to cross gap junctions both NS neurons are dye-coupled and extend a profuse neuritic tree (Fig. 1B). Each NS neuron sends branches through the ipsilateral and contralateral nerve roots and through ipsilateral anterior and posterior connective nerves leading to adjacent ganglia. Thus the pair of NS neurons are dye- and electrically-coupled (Fig. 1C) with a high coupling

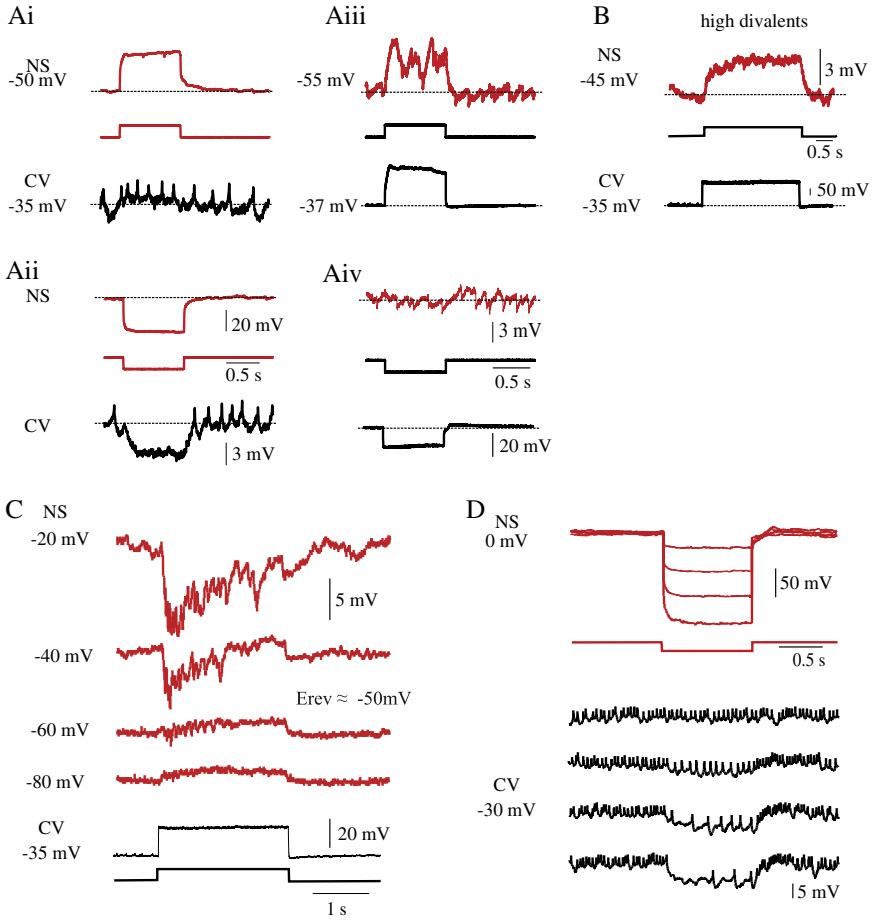

Fig. 2. NS is linked to MNs via rectifying junctions and chemical synapses. (A) Responses of an NS and a CV motoneuron to current pulses injected in either cell. The traces show simultaneous intracellular recordings of both neurons in a single isolated ganglion. In the four panels the upper traces show NS recordings (red traces in this and the rest of the figures); the lower traces show the CV recordings and the intermediate recordings indicate the current injection of +2 nA in NS (Ai) or CV (Aiii), and −2 nA in NS (Aii) or CV (Aiv). (B) Response of an NS neuron to the stimulation of a CV motoneuron in a solution with a high divalent ion concentration. (C) Responses of an NS neuron to the stimulation of a CV motoneuron in normal saline as Vm_{NS} was set at different values, indicated on the left. The line below the CV traces indicates the timing of the current injection. (D) In dual intracellular recordings Vm_{NS} was set at 0 mV and Vm_{CV} at −30 mV. A series of hyperpolarizing pulses (−2 to −8 nA, at 2 nA intervals) were injected in NS that gradually hyperpolarized CV and reduced its firing frequency. The line below the NS traces indicates the timing of the current injection. Adapted from Rela and Szczupak, 2003, 2007.

coefficient (Wadepuhl, 1989) that turns them into a single unit for a variety of electrophysiological signals (Rela and Szczupak, 2003).

Although NS neurons do not fire sodium dependent action potentials they are not ruled exclusively by their passive properties. These cells express a variety of voltage activated conductances that mediate highly effective propagation of graded signals (Rela et al., 2009; Yang et al., 2013).

The pair of NS neurons are connected to every excitatory motoneuron through rectifying electrical junctions (Wadepuhl, 1989). Fig. 2A illustrates the interactions between NS and one specific MN, the excitor of circular ventral (CV) muscle fibre. With both neurons at their resting potential, sequential injection of positive and negative electrical current pulses in each neuron reveals that NS transmits only hyperpolarizing signals to CV (Fig. 2Ai and Aii) and CV transmits a mixture of depolarizing and hyperpolarizing signals when excited, but no signal when it is hyperpolarized (Fig. 2Aiii and iv). What is the origin of the two opposing signals delivered by the excited MN?

In addition to the electrical junctions, the MNs are linked to the NS neurons through chemical synapses that exhibit a reversal potential at around −50 mV (Wadepuhl, 1989; Rela and Szczupak, 2003). The interaction is not direct but is mediated by interneurons with processes that run along the nerve cord (cord-spanning). Fig. 2B shows the response of an NS neuron to CV stimulation in the presence of a solution containing a high divalent ion concentration (high Mg^{2+} and high Ca^{2+}) that impairs polysynaptic transmission (Nicholls and Purves, 1970). In this condition the response of NS to excitation of the MN is purely depolarizing, revealing the sole effect of the rectifying electrical junctions. In normal saline, the NS response to the MN excitation is a hyperpolarization that can counteract the signal transmitted through the electrical synapses (Fig. 2Aiii). When the membrane potential of NS (Vm_{NS}) is close to the reversal potential of the chemical synapse its influence is negligible, and the signal through the electrical synapse predominates. But as the driving force of the chemical synapse is magnified its influence becomes larger than the electrical signal and a net hyperpolarization is observed (Fig. 2C).

The rectifying gap junctions connecting NS to the excitatory MNs conduct at a transjunctional potential ($Vj = Vm_{NS} - Vm_{MN}$) below 0–15 mV (Rela and Szczupak, 2007; Rodriguez et al., 2009). Fig. 2D shows a recording in which increasing the hyperpolarization of NS evoked an increasing hyperpolarization of CV and reduced its firing frequency. By virtue of this interaction the MN firing frequency becomes a linear relationship of Vm_{NS} starting at a $Vj = 0$ mV (Rela and Szczupak, 2007). A similar analysis performed for other MNs showed similar results (Iscla et al., 1999; Rodriguez et al., 2009).

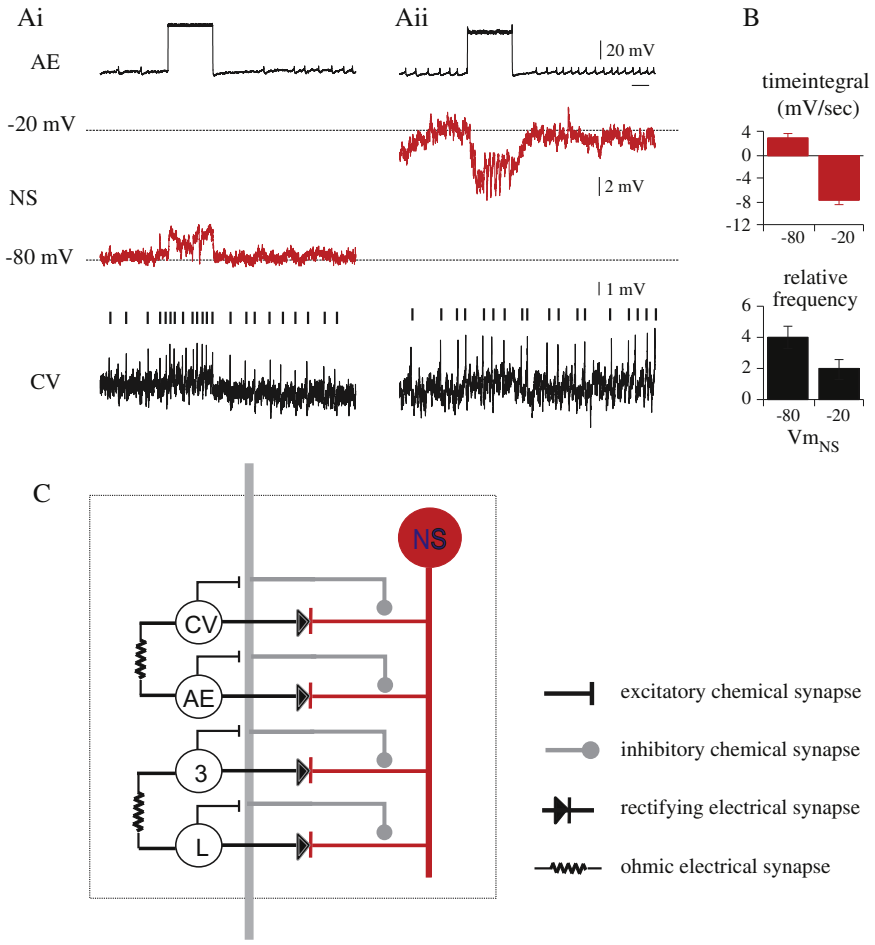

Fig. 3. NS regulates the coupling among MNs. (A) The traces show the intracellular recordings of AE (top), NS (middle, in red) and CV (bottom) neurons, as AE was stimulated with a square pulse. The short vertical lines above the CV recording indicate the timing of each spike. The recordings were performed with Vm_{NS} at −80 (Ai) and at −20 mV (Aii). (B) The red bars describe the time-integral of the responses of NS at −80 and at −20 mV. The black bars describe the relative firing frequency of CV at the two NS conditions. The firing frequency of CV during the AE pulse was made relative to this variable before the pulse (firing during the pulse divided by the firing before the pulse). A and B are adapted from Rela and Szczupak, 2003. (C) Scheme of the MN (in black) circuit centered around the NS (in red) neuron including a cord spanning interneuron (in gray). The square indicates the ganglion boundary. CV and AE motoneurons, and DE-3 and MN-L are electrically coupled through relatively ohmic junctions, while the four MNs are electrically coupled to NS through rectifying junctions. The MNs are also linked to NS via inhibitory chemical synapses.

The circuitry described indicates that NS cells are hyperpolarized by the MNs through chemical synapses and can transmit this hyperpolarizing signal back to the MNs by means of the rectifying electrical junctions. Is this recurrent inhibitory circuit effective?

To answer this question Lorena Rela performed an analysis of the cross-talk between pairs of heteronymous MNs while manipulating Vm_{NS}. Fig. 2C indicates that the magnitude of the hyperpolarizing signal depends on Vm_{NS} and therefore the magnitude of the signal transmitted through the gap junctions will depend on Vm_{NS}. Two pairs of MNs were studied: (i) the excitor of the annulus erector (AE) and the CV motoneuron (Rela and Szczupak, 2003) and (ii) the excitor of dorsal longitudinal muscles 3 (DE-3), and the excitor of dorsal and ventral longitudinal muscles (MN-L) (Rodriguez et al., 2009).

Let us consider as an example the AE and CV case. Fig. 3A shows responses of CV and NS to AE motoneuron stimulation while setting Vm_{NS} below (−80 mV) or above (−20 mV) the reversal potential of the hyperpolarizing signal. With Vm_{NS} at −80 mV NS was depolarized and CV increased its firing rate during AE excitation (Fig. 3Ai and B). With Vm_{NS} at −20 mV NS was hyperpolarized but the CV firing rate during AE stimulation was unaffected (Fig. 3 Aii and B). These results suggest that AE and CV motoneurons are electrically coupled, which was confirmed by analyzing their interaction in a high Mg^{2+}–low Ca^{2+} solution (Rela and Szczupak, 2003). In this condition, that precludes chemical synaptic interactions, AE and CV were interconnected by a relatively ohmic conductance (where the conductance is relatively insensitive to the polarity of the junction potential; (Rela and Szczupak, 2003). The results obtained for the AE and CV pair were homologous to those obtained with the DE-3 and MN-L pair (Rela and Szczupak, 2003; Rodriguez et al., 2009).

These series of experiments taught us that heteronymous MNs in the leech are electrically coupled. The coupling is weak, but it is sufficient to affect the firing frequency of the MNs, and the expression of this coupling depends on the membrane potential of the premotor NS neuron. Thus NS orchestrates a recurrent inhibitory network (Fig. 3C) that can effectively counteract the cross talk among electrically-coupled MNs.

While the electrical synapses act only locally, the hyperpolarizing inputs onto NS can be transmitted from MNs in other segments though cord-spanning interneuron(s) (Rela and Szczupak, 2003) and therefore the recurrent inhibition could act beyond the local circuit, an aspect that has not been explored so far.

4. NS in motor behaviors

Having established the NS circuit in basal conditions the natural question to ask is how does it operate in the context of motor

behaviors. The leech displays two main locomotive behaviors, swimming and crawling, that are executed by the rhythmic contraction and relaxation of the muscles that compose its body wall (Kristan et al., 2005). Leeches swim by undulating their body in the dorso-ventral plane. This is achieved by the antiphasic rhythmic activity of excitors of dorsal and ventral longitudinal muscles (Gray et al., 1938; Stent et al., 1978). Leeches crawl on solid substrate by performing sequential elongation and contraction waves of their body, coordinated with attachment and release of their front and rear suckers (Gray et al., 1938; Stern-Tomlinson et al., 1986). The elongation and contraction waves are achieved by contraction of circular and longitudinal muscles, respectively (Eisenhart et al., 2000). Swimming is a relatively fast (around 1 Hz) locomotor behavior (Kristan et al., 1974), while crawling is a much slower (around 0.1 Hz) displacement and allows exploratory intervals (Gray et al., 1938; Stern-Tomlinson et al., 1986).

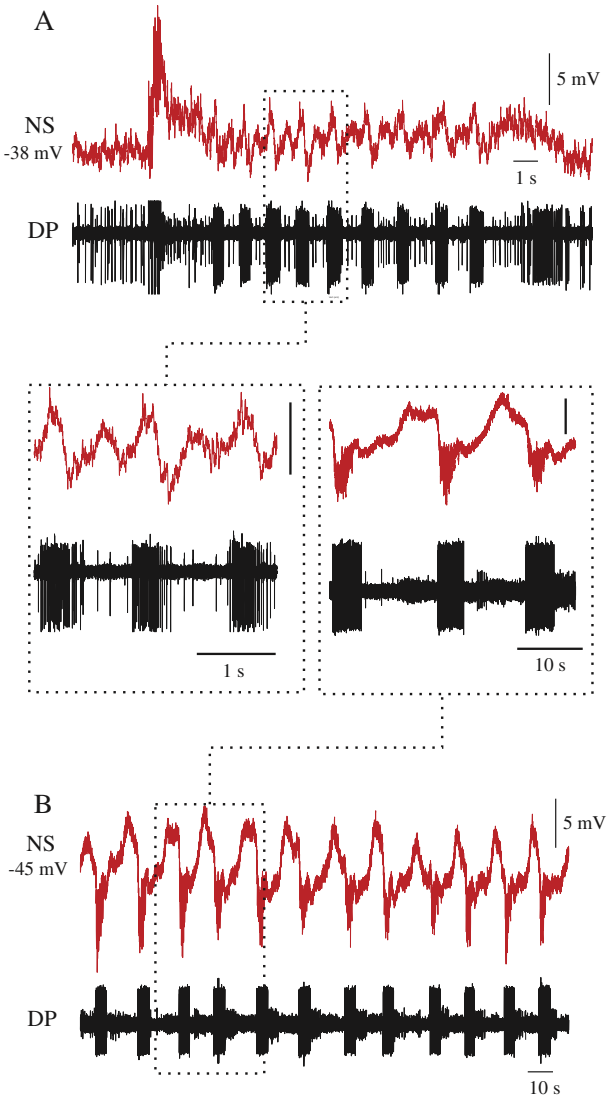

Fig. 4. NS membrane potential oscillates during rhythmic motor patterns. Rhythmic motor patterns, typical of swimming and crawling, were monitored by extracellular recordings of the activity of DE-3 motoneurons in dorsal posterior (DP) root nerves. The upper traces show the intracellular recording of NS (in red) and the lower trace the extracellular DP recording during swimming (A) and crawling (B). In between A and B an expanded views of a segment of each panel is shown: vertical scales indicate 5 mV. Swimming was elicited in a chain of ganglia (G2 to tail brain) by electrical stimulation of a posterior DP root. Crawling was evoked in isolated ganglia by perfusion with a solution containing 75 μM dopamine. Adapted from Rodriguez et al., 2012.

Both motor patterns can be elicited in the isolated nerve cord using the activity of the DE-3 motoneuron as a read out (Kristan et al., 1974; Baader, 1997; Eisenhart et al., 2000). DE-3 spikes can be recorded extracellularly in the DP nerve (Ort et al., 1974). During swimming (Fig. 4A) the DE-3 burst signals the dorsal contraction and the silent period indicates the ventral contraction phase; during crawling (Fig. 4B) the DE-3 burst indicates the contraction phase, and the silent period includes elongation and positioning of the suckers.

NS membrane potential oscillates in phase with both motor patterns (Fig. 4). During swimming Vm_{NS} displays two sequential hyperpolarization – depolarization shifts per cycle (Fig. 4A), while during crawling it shows a hyperpolarization in phase with DE-3 (Fig. 4B) and a depolarization in phase with CV, which is responsible for the elongation phase of crawling (Rodriguez et al., 2012).

Because NS receives inputs from all the excitatory MNs in the ganglion this cell can be considered a readout of motor activity. Since different MNs are active throughout both motor patterns it was expected that the NS neurons remain bombarded with hyperpolarizing signals all through the episode. Instead, Vm_{NS} exhibits regular positive and negative shifts tuned to each rhythmic activity. This suggests that, in the behavioral context, the functional synaptic weight of different MN–NS pairs is modulated differentially, and therefore the synaptic input from different MNs is not uniformly expressed.

During swimming each segment performs movements that maintain bilateral (left–right) symmetry, but dorso-ventral asymmetry; during crawling, instead, the movements are symmetrical in both axes. The Vm_{NS} oscillations reflect this distribution of motor activity in time: during swimming Vm_{NS} displays two hyperpolarizing shifts per cycle, in phase with the sequential excitation of the dorsal and ventral longitudinal excitors; during crawling the single hyperpolarization shift is tuned with the simultaneous excitation of these two groups of motoneurons. This analysis suggests that during motor behaviors dorsal and ventral longitudinal excitors transmit the strongest hyperpolarizing signals.

5. NS influence on motor behaviors

Having characterized the activity of NS during swimming and crawling the next natural question is what is its contribution to these motor patterns. Manipulation of Vm_{NS} during swimming had no effect on the rhythm period nor on the MN firing frequency but had marked effect on dopamine-elicited crawling in isolated ganglia (Rodriguez et al., 2012).

Fig. 5 shows two segments of a dorsal posterior (DP) nerve recording during crawling where negative and positive 1-nA current pulses were injected in NS. Injection of −1-nA caused a dual effect: it slowed down the rhythm and it lowered DE-3 firing frequency (Fig. 5A). On the other hand, injection of +1 nA had no effect on the cycle frequency but caused an increase in DE-3 firing frequency (Fig. 5C).

These results indicate that in the context of this motor pattern NS retains its influence on the firing frequency of the MN, but it also shows that NS has a direct influence on the central pattern generator (CPG) responsible for crawling. The fact that depolarization of NS caused an increase in the MN firing frequency suggests that the recurrent inhibitory circuit is functional during crawling. With no influence on the period of the motor pattern, depolarization of NS affects the DE-3 output. We interpret that shifting Vm_{NS} to a more positive level pushed the junctional potential to a value that inactivated the NS–MN coupling. When the electrical junction is inactivated the hyperpolarization of NS that occurs in phase with DE-3 bursts (Fig. 4B), lacks the power to feedback onto the MN,

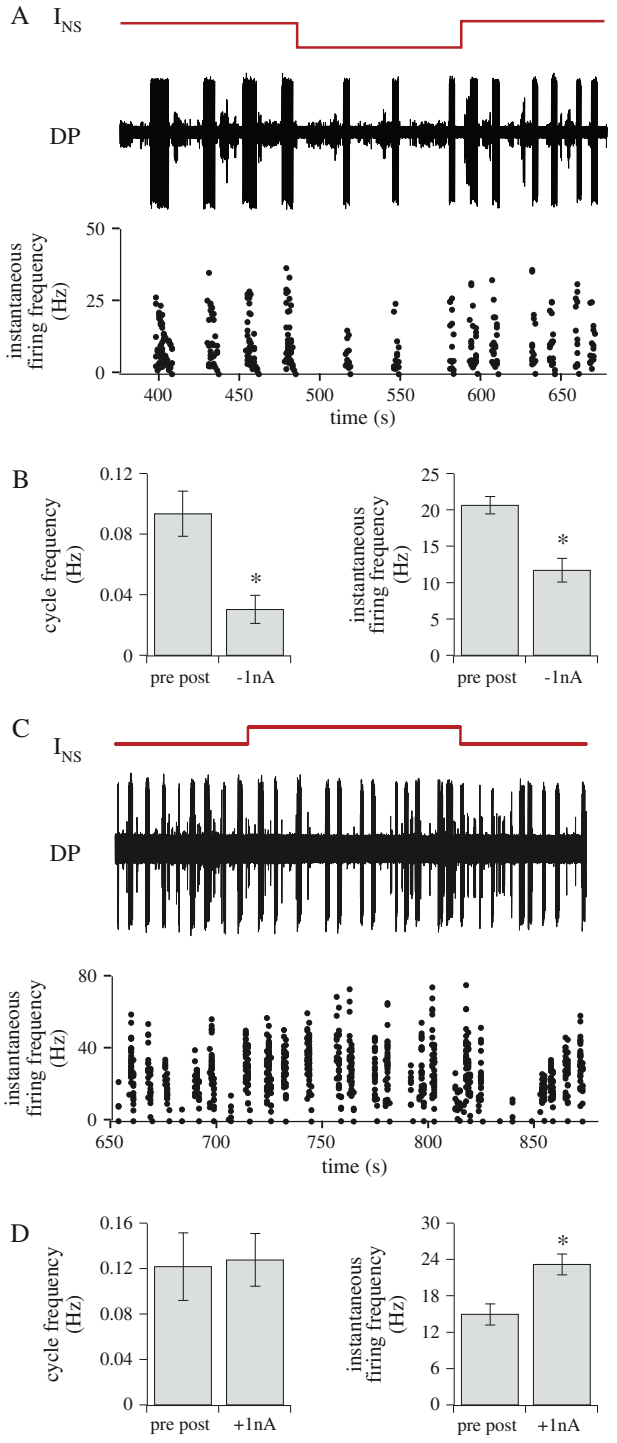

Fig. 5. NS modulates crawling. (A) The traces show an extracellular DE-3 recording in a DP nerve during a dopamine-induced crawling episode. The upper red line indicates the timing of the injection of a −1-nA electrical pulse into NS (I_{NS}). The graph shows the instantaneous firing frequency of each spike as a function of time (at 0 s the dopamine perfusion was initiated). (B) The bars indicate the mean cycle frequency (1/period) and the mean instantaneous frequency measured before and after (pre post) the pulse, and during the pulse (−1). (C and D) As A and B for a +1-nA pulse. * Stands for $p < 0.001$ for paired t-test. Adapted from Rodriguez et al., 2012.

truncating the recurrent inhibition. In the absence of the inhibitory signal DE-3 firing frequency increased.

When NS was hyperpolarized the most prominent effect was its influence on the CPG, suggesting that this rhythmogenic circuit could be formed by MNs, and indeed, preliminary data indicates that the CV motoneuron is part of the crawling CPG (Schneider and Szczupak, unpublished results). Then the reduction in the firing frequency of DE-3 in this condition could be due to a direct effect of NS on the MN, a indirect effect via the CPG or to both.

6. Motor recurrent inhibition in perspective

From the description of the Renshaw and NS circuits that has been presented it is interesting to notice that recurrent inhibition in the motor system of the leech exhibits major analogies with that of vertebrates.

- *NS and Renshaw cells occupy a similar locus in the network:* they are pre and postsynaptic to the MNs. In Renshaw cells input and output are mediated by chemical synapses, in the leech a mixture of chemical and electrical synapses interconnect NS and MNs.
- In vertebrates, recurrent inhibition is distributed between homonymous and heteronymous motor groups and a Renshaw cell receives inputs from different motor groups. NS represents an extreme case of this pattern, since it is linked to all the excitatory motoneurons in the ganglion.
- NS and Renshaw membrane potential oscillate in phase with rhythmic motor patterns activated in the isolated nervous system.
- *Renshaw cells are phase-specific:* different individual neurons are activated at specific phases of the motor pattern. There is only one pair of NS neuron per ganglion, but yet the different phases of the motor patterns are reflected in the membrane potential oscillations.

The relative simplicity of the leech nervous system, the ability to record identified neurons from preparation to preparation, and the fact that stimulating and silencing individual neurons affect behavioral outputs favor a functional analysis that has been more elusive in other organism. The recurrent inhibitory circuit centered around the NS neuron was shown to influence the motor system in two different – but not independent – ways: (1) it regulates the degree of coupling among heteronymous MNs and (2) it exerts a recurrent control on the level of MN activation during rhythmic activity. In addition, NS can regulate the period of rhythmic activity, probably because the CPG is, at least, partly composed of MNs. Renshaw cells are in a position to play similar roles, but the right experiments wait to be performed.

Acknowledgments

The author thanks Dr. Martín Carbó Tano and Dr. Fernando Marengo for their critical evaluation of the present manuscript. The work is supported by Grants from University of Buenos Aires (UBACyT) and from Agencia Nacional de Promoción Científica y Tecnológica (Argentina) to LS.

References

Alvarez, F.J., Fyffe, R.E., 2007. The continuing case for the Renshaw cell. J. Physiol. 584, 31–45.
Baader, A.P., 1997. Interneuronal and motor patterns during crawling behavior of semi-intact leeches. J. Exp. Biol. 200, 1369–1381.
Bizzi, E., Tresch, M.C., Saltiel, P., dÁvella, A., 2000. New perspectives on spinal motor systems. Nat. Rev. Neurosci. 1, 101–108.
Brink, E.E., Suzuki, I., 1987. Recurrent inhibitory connexions among neck motoneurones in the cat. J. Physiol. 383, 301–326.
Brodfuehrer, P.D., Friesen, W.O., 1986. Initiation of swimming activity by trigger neurons in the leech subesophageal ganglion. I. Output connections of Tr1 and Tr2. J. Comp. Physiol. 159, 489–502.
Burrows, M., 1992. Local circuits for the control of leg movements in an insect. TINS 15, 226–232.
Buschges, A., Akay, T., Gabriel, J.P., Schmidt, J., 2008. Organizing network action for locomotion: insights from studying insect walking. Brain Res. Rev. 57, 162–171.

Buschges, A., Scholz, H., El Manira, A., 2011. New moves in motor control. Curr. Biol. 21, R513–R524.
Cannon, W.B., 1929. Organization for physiological homeostasis. Physiol. Rev. 9, 399–431.
Clarac, F., Cattaert, D., Le Ray, D., 2000. Central control components of a´simplé stretch reflex. TINS 23, 199–208.
Eccles, J.C., Fatt, P., Koketsu, K., 1954. Cholinergic and inhibitory synapses in a pathway from motor-axon collaterals to motoneurons. J. Physiol. 126, 524–562.
Edwards, D.H., Heitler, W.J., Krasne, F.B., 1999. Fifty years of a command neuron: the neurobiology of escape behavior in the crayfish. TINS 22, 153–161.
Eisenhart, F.J., Cacciatore, T.W., Kristan, W.B., 2000. A central pattern generator underlies crawling in the medicinal leech. J. Comp. Physiol. A 186, 631–643.
Frank, E., Jansen, J.K.S., Rinvik, E., 1975. A multisomatic axon in the central nervous system of the leech. J. Comp. Neurol. 159, 1–14.
Gray, J., Lissmann, H.W., Pumphrey, R.J., 1938. The mechanism of locomotion in the leech (*Hirudo medicinalis Ray*). J. Exp. Biol. 15, 408–430.
Graziano, M.S., Taylor, C.S., Moore, T., 2002a. Complex movements evoked by microstimulation of precentral cortex. Neuron 34, 841–851.
Graziano, M.S.A., Taylor, C.S.R., Moore, T., Cooke, D.F., 2002b. The cortical control of movement revisited. Neuron 38, 349–362.
Grillner, S., 2003. The motor infrastructure: from ion channels to neuronal networks. Nat. Rev. Neurosci. 4, 573–586.
Hamm, T.M., 1990. Recurrent inhibition to and from motoneurons innervating the flexor digitorum and flexor hallucis longus muscles of the cat. J. Neurophysiol. 63, 395–403.
Hultborn, H., 2006. Spinal reflexes, mechanisms and concepts: from Eccles to Lundberg and beyond. Prog. Neurobiol. 78, 215–232.
Iscla, I.R., Arini, P.D., Szczupak, L., 1999. Differential channeling of sensory stimuli onto a motor neuron in the leech. J. Comp. Physiol. 184, 233–241.
Kristan, W.B., Stent, G.S., Ort, C.A., 1974. Neuronal control of swimming in the medicinal leech: I. Dynamics of the swimming rhythm. J. Comp. Physiol. 94, 97–119.
Kristan Jr., W.B., Calabrese, R.L., Friesen, W.O., 2005. Neuronal control of leech behavior. Prog. Neurobiol. 76, 279–327.
Lockery, S.R., Wittenberg, G., Kristan, W.B., Cottrell, G.W., 1989. Function of identified interneurons in the leech elucidated using neural networks trained by back-propagation. Nature 340, 468–471.
Mann, K.H., 1962. Leeches (Hirudinae). Their Structure, Physiology, Ecology and Embryology. Pergamon Press, New York.
Marder, E., Goaillard, J.M., 2006. Variability, compensation and homeostasis in neuron and network function. Nat. Rev. Neurosci. 7, 563–574.
McCrea, D.A., 2001. Spinal circuitry of sensorimotor control of locomotion. J. Physiol. 533 (1), 44–50.
McCrea, D.A., Pratt, C.A., Jordan, L.M., 1980. Renshaw cell activity and recurrent effects on motoneurons during fictive locomotion. J. Neurophysiol. 44, 475–488.
Muller, K.J., Nicholls, J.G., Stent, G.S., 1981. Neurobiology of the Leech. Cold Spring Harbor Laboratory, Cold Spring Harbor, NY.
Mulloney, B., Smarandache-Wellmann, C., 2012. Neurobiology of the crustacean swimmeret system. Prog. Neurobiol. 96, 242–267.
Nicholls, J.G., Baylor, D.A., 1968. Specific modalities and receptive fields of sensory neurons in CNS of the leech. J. Neurophysiol. 31, 740–756.
Nicholls, J.G., Purves, D., 1970. Monosynaptic chemical and electrical connexions between sensory and motor cells in the central nervous system of the leech. J. Physiol. 209, 647–667.
Nishimaru, H., Restrepo, C.E., Kiehn, O., 2006. Activity of Renshaw cells during locomotor-like rhythmic activity in the isolated spinal cord of neonatal mice. J. Neurosci. 26, 5320–5328.
Orlovsky, G.N., Deliagina, T.G., Grillner, S., 1999. Neuronal Control of Locomotion. Oxford University Press.
Ort, C.A., Kristan, W.B., Stent, G.S., 1974. Neuronal control of swimming in the medicinal leech. J. Comp. Physiol. A 94, 121–154.
Poppele, R.B.G., 2003. Sophisticated spinal contributions to motor control. TINS 26, 269–276.
Pratt, C.A., Jordan, L.M., 1987. Ia inhibitory interneurons and Renshaw cells as contributors to the spinal mechanisms of fictive locomotion. J. Neurophysiol. 57, 56–71.
Rela, L., Szczupak, L., 2003. Coactivation of motoneurons regulated by a network combining electrical and chemical synapses. J. Neurosci. 23, 682–692.
Rela, L., Szczupak, L., 2007. In situ characterization of a rectifying electrical junction. J. Neurophysiol. 97, 1405–1412.
Rela, L., Yang, S.M., Szczupak, L., 2009. Calcium spikes in a leech nonspiking neuron. J. Comp. Physiol. 195, 139–150.
Renshaw, B., 1941. Influence of discharge of motoneurons upon excitation of neighbouring motoneurons. J. Neurophysiol. 4, 167–183.
Rodriguez, M.J., Perez-Etchegoyen, C.B., Szczupak, L., 2009. Premotor nonspiking neurons regulate coupling among motoneurons that innervate overlapping muscle fiber population. J. Comp. Physiol. A 195, 1432–1451.
Rodriguez, M.J., Alvarez, R.J., Szczupak, L., 2012. Effect of a nonspiking neuron on motor patterns of the leech. J. Neurophysiol. 107, 1917–1924.
Stein, P.S.G., 1978. Motor systems, with specific reference to the control of locomotion. Annu. Rev. Neurosci. 1, 61–81.
Stent, G.S., Kristan, W.B., Friesen, W.O., Ort, C.A., Poon, M., Calabrese, R.L., 1978. Neuronal generation of the leech swimming movement. An oscillatory network of neurons driving a locomotory rhythm has been identified. Science 200, 1348–1357.
Stern-Tomlinson, W., Nusbaum, M.P., Perez, L.E., Kristan, W.B., 1986. A kinematic study of crawling behavior in the leech, *Hirudo medicinalis*. J. Comp. Physiol. A 158, 593–603.
Stuart, A.E., 1970. Physiological and morphological properties of motoneurones in the central nervous system of the leech. J. Physiol. 209, 627–646.
Turrigiano, G.G., 1999. Homeostatic plasticity in neuronal networks: the more things change, the more they stay the same. Trends Neurosci. 22, 221–227.
Wadepuhl, M., 1989. Depression of excitatory motoneurones by a single neurone in the leech central nervous system. J. Exp. Biol. 143, 509–527.
Yang, S.M., Vilarchao, M.E., Rela, L., Szczupak, L., 2013. Wide propagation of graded signals in nonspiking neurons. J. Neurophysiol. 109, 711–720.