Review paper

Recurrent inhibition in motor systems, a comparative analysis

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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

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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.

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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

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.

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
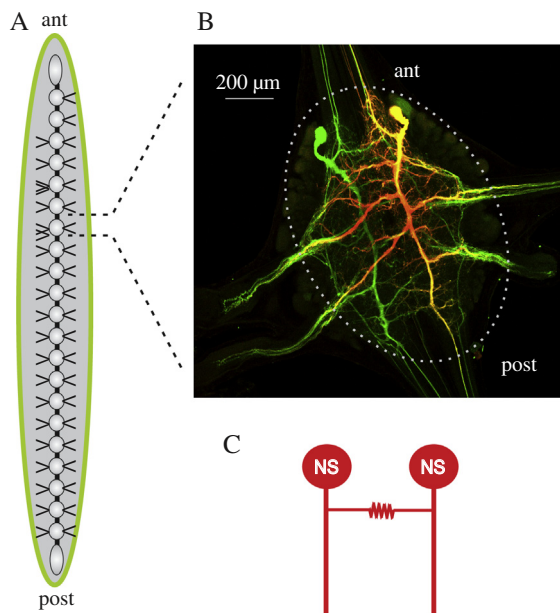

Fig. 1. Anatomy of NS neurons. (A) Scheme of *Hirudo* nervous system, composed of a chain of 21 midbody ganglia (represented by circles), flanked by a head and a tail brain (represented by ovals). (B) Confocal image of a ganglion (whose approximate outline is marked by dotted line) where one of the NS 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).