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Review

Initiation of locomotion in lampreys

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ABSTRACT

The spinal circuitry underlying the generation of basic locomotor synergies has been described in substantial detail in lampreys and the cellular mechanisms have been identified. The initiation of locomotion, on the other hand, relies on supraspinal networks and the cellular mechanisms involved are only beginning to be understood. This review examines some of the findings relative to the neural mechanisms involved in the initiation of locomotion of lampreys. Locomotion can be elicited by sensory stimulation or by internal cues associated with fundamental needs of the animal such as food seeking, exploration, and mating. We have described mechanisms by which escape swimming is elicited in lampreys in response to mechanical skin stimulation. A rather simple neural connectivity is involved, including sensory and relay neurons, as well as the brainstem rhombencephalic reticulospinal cells, which act as command neurons. We have shown that reticulospinal cells have intrinsic membrane properties that allow them to transform a short duration sensory input into a long-lasting excitatory command that activates the spinal locomotor networks. These mechanisms constitute an important feature for the activation of escape swimming. Other sensory inputs can also elicit locomotion in lampreys. For instance, we have recently shown that olfactory signals evoke sustained depolarizations in reticulospinal neurons and chemical activation of the olfactory bulbs with local injections of glutamate induces fictive locomotion. The mechanisms by which internal cues initiate locomotion are less understood. Our research has focused on one particular locomotor center in the brainstem, the mesencephalic locomotor region (MLR). The MLR is believed to channel inputs from many brain regions to generate goal-directed locomotion. It activates reticulospinal cells to elicit locomotor output in a graded fashion contrary to escape locomotor bouts, which are all-or-none. MLR inputs to reticulospinal cells use both glutamatergic and cholinergic transmission; nicotinic receptors on reticulospinal cells are involved. MLR excitatory inputs to reticulospinal cells in the middle (MRRN) are larger than those in the posterior rhombencephalic reticular nucleus (PRRN). Moreover at low stimulation strength, reticulospinal cells in the MRRN are activated first, whereas those in

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the PRRN require stronger stimulation strengths. The output from the MLR on one side activates reticulospinal neurons on both sides in a highly symmetrical fashion. This could account for the symmetrical bilateral locomotor output evoked during unilateral stimulation of the MLR in all animal species tested to date. Interestingly, muscarinic receptor activation reduces sensory inputs to reticulospinal neurons and, under natural conditions, the activation of MLR cholinergic neurons will likely reduce sensory inflow. Moreover, exposing the brainstem to muscarinic agonists generates sustained recurring depolarizations in reticulospinal neurons through pre-reticular effects. Cells in the caudal half of the rhombencephalon appear to be involved and we propose that the activation of these muscarinoceptive cells could provide additional excitation to reticulospinal cells when the MLR is activated under natural conditions. One important question relates to sources of inputs to the MLR. We found that substance P excites the MLR, whereas GABA inputs tonically maintain the MLR inhibited and removal of this inhibition initiates locomotion. Other locomotor centers exist such as a region in the ventral thalamus projecting directly to reticulospinal cells. This region, referred to as the diencephalic locomotor region, receives inputs from several areas in the forebrain and is likely important for goal-directed locomotion. In summary, this review focuses on the most recent findings relative to initiation of lamprey locomotion in response to sensory and internal cues in lampreys.

Contents

1. The lamprey nervous system as a tool to examine the cellular bases of vertebrate locomotor behavior

Lampreys are early vertebrates that have evolved from the main vertebrate line some 450 million years ago. The general organization of their nervous system is highly similar to that of other vertebrates, including mammals. The lamprey model has been used for nearly three decades to identify the cellular mechanisms involved in the generation and control of vertebrate locomotion. A major benefit of this animal model is the comparative simplicity of its nervous system relative to that of mammals. This was foreseen as a marked advantage to identify the detailed synaptic connectivity and the intrinsic properties of neurons involved in locomotor behavior. The possibility of isolating and maintaining the entire central nervous system in physiological conditions *in vitro* for many hours up to a few days became a significant additional advantage of the lamprey preparation. The early work of Carl Rovainen established some of the connectivity within the spinal cord and lower brainstem of lampreys (Rovainen, 1967, 1974b, 1979a,b). The lamprey nervous system proved its considerable value as an experimental model for understanding the neural bases of locomotion (Grillner and Wallén, 1985; Grillner et al., 1981, 1983a,b) when the group of Sten Grillner identified, for the first time in a vertebrate species, the detailed spinal circuitry responsible for the segmental generation of locomotion (Buchanan and Grillner, 1987, for reviews see Grillner et al., 1995, 1998). At that time, however, there was still very little information about the neural mechanisms underlying the initiation and control of locomotor activity in these animals (Kasicki and Grillner, 1986; Kasicki et al., 1989; McClellan and Grillner, 1984). Research on the supraspinal control of lamprey locomotion has increased over the last 15 years and there have been significant gains in knowledge.

Locomotion can be triggered by sensory inputs as lampreys react vigorously to sensory cues to generate either escape behavior (Fig. 1) or locomotion directed towards a specific target in their environment (for a review see Rossignol et al., 2006). Locomotion can also be elicited by internal cues in specific behavioral contexts such as exploration, food seeking, and reproduction. Nevertheless, locomotion relies on supraspinal structures whether activated by internal cues or in response to sensory inputs. In lampreys, the brainstem contains reticulospinal cells that act as command neurons to initiate locomotor activity by directly activating networks in the spinal cord (Buchanan and Cohen, 1982; Buchanan et al., 1987; McClellan, 1986, 1987, 1988; Ohta and Grillner, 1989; Rovainen, 1974a, 1978, 1979b; Viana Di Prisco et al., 1997, 2000). To elicit locomotion under any circumstance, reticulospinal cells constitute the main and final common descending pathway capable of activating the spinal locomotor networks.

2. Reticulospinal neurons in lampreys

There have been several studies examining lamprey reticulospinal cells both anatomically and physiologically. In an elegant series of studies, Carl Rovainen described the basic physiological organization of the reticulospinal system (Homma and Rovainen, 1978; Rovainen, 1967, 1974b, 1978, 1979a,b, 1982; Rovainen et al., 1973). Reticulospinal cells are located within four distinct brainstem reticular nuclei. The most rostral group is located within the mesencephalon, the mesencephalic reticular nucleus (MRN). It contains about 90 reticulospinal cells on each side in adult lampreys (*Ichthyomyzon unicuspis*), all of which project to the ipsilateral spinal cord (Bussières, 1994; for a review, see Brodin et al., 1988). The largest reticulospinal cells project as far down as the caudal end of the spinal cord. In the rhombencephalon, there are three reticular nuclei, all of which contain cells projecting to the spinal cord. The most rostral group is referred to as the anterior rhombencephalic reticular nuclei and contains about 90 cells in adult lampreys, with about 30% projecting contralaterally. More caudally, there are two reticular nuclei, which combined contain approximately 90% of all reticulospinal cells. The middle rhombencephalic reticular nucleus has approximately 330 reticulospinal cells with 20% projecting to the contralateral side, including the Mauthner cells, which send a prominent axon in the dorsolateral aspect of the spinal cord (Rovainen, 1967). More caudally, there is a large group of reticulospinal cells extending rostrocaudally through most of the caudal half of the rhombencephalon. There are approximately 730 reticulospinal cells located in this nucleus in adult lampreys with about 16% projecting contralaterally.

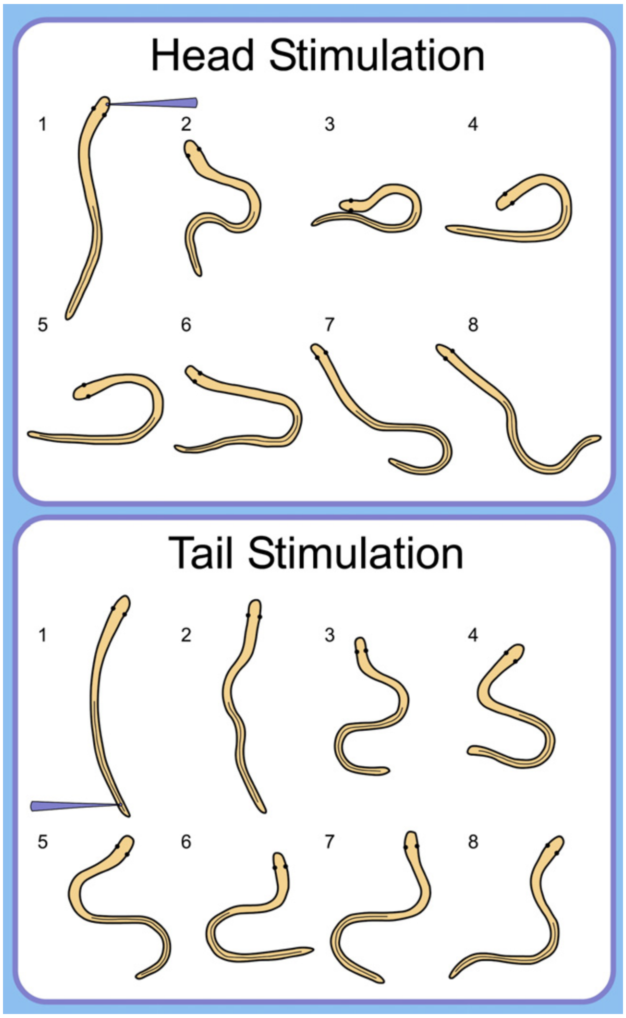

Fig. 1 – Schematic drawings representing the time sequence of a motor response elicited by mechanical stimulation of the skin over the head region (top) and tail region (bottom). The cartoons illustrate only the early part of the motor response that was followed, in all cases, by a locomotor bout of variable duration. The cartoons are numbered sequentially as the movements occurred in time.

Reticulospinal cells constitute most of the descending projections to the spinal cord of lampreys (more than 90% of the descending axons) and therefore their role in initiation and control of locomotion is pivotal. Although Ronan (1989) reported cells in the diencephalon projecting to the spinal cord, most of the remaining descending axons in lampreys originate from vestibulospinal cells with somata located at the lateral edge of the rhombencephalon and axons projecting to the ipsi- and contralateral spinal cord. Vestibulospinal cells are rhythmically active during locomotion of lampreys (Bussières and Dubuc, 1992a). Their exact role in the control of locomotor activity has not been established yet. A recent study by Zelenin et al. (2003) indicates that they would have preferential actions on the rostral spinal cord in opposition to reticulospinal cells which act on the entire cord. In addition to their role in the supraspinal control of locomotion, reticulospinal cells are crucial for postural adjustments of these animals. They receive powerful vestibular inputs (Rovainen, 1979a; Bussières and Dubuc, 1992b; Bussières et al., 1999; Deliagina et al., 1992; Pflieger and Dubuc, 2004), which constitute signals for postural adjustments (for reviews, see Deliagina et al., 2002; Deliagina and Orlovsky, 2002; Grillner et al., 1995). The contribution of reticulospinal cells in equilibrium and postural control has been elegantly described by the group of Deliagina and Orlovsky with combined behavioral and physiological approaches (see the contribution of T. Deliagina et al., in this journal issue). Reticulospinal cells are therefore likely to provide a dual descending input involved in generating locomotor activity and providing postural and equilibrium control.

3. Sensory-evoked locomotion in lampreys

Mechanical stimulation of the skin elicits escape locomotion in lampreys by activating reticulospinal cells (Viana Di Prisco et al., 1997, 2000). A mechanical stimulus applied to the body or tail elicits discharges in primary afferent fibers that have their cell bodies located within the spinal cord (Christenson et al., 1988a,b; Brodin et al., 1987; Finger and Rovainen, 1982; Teravainen and Rovainen, 1971). These neurons were named dorsal cells and they respond among other things to mechanical pressure applied to the skin. The information is then carried through the dorsal columns to the dorsal column nuclei located in the caudal brainstem (Dubuc et al., 1993a,b). The dorsal column nuclei, in turn, send direct projections to reticulospinal cells. Information from the skin of the head

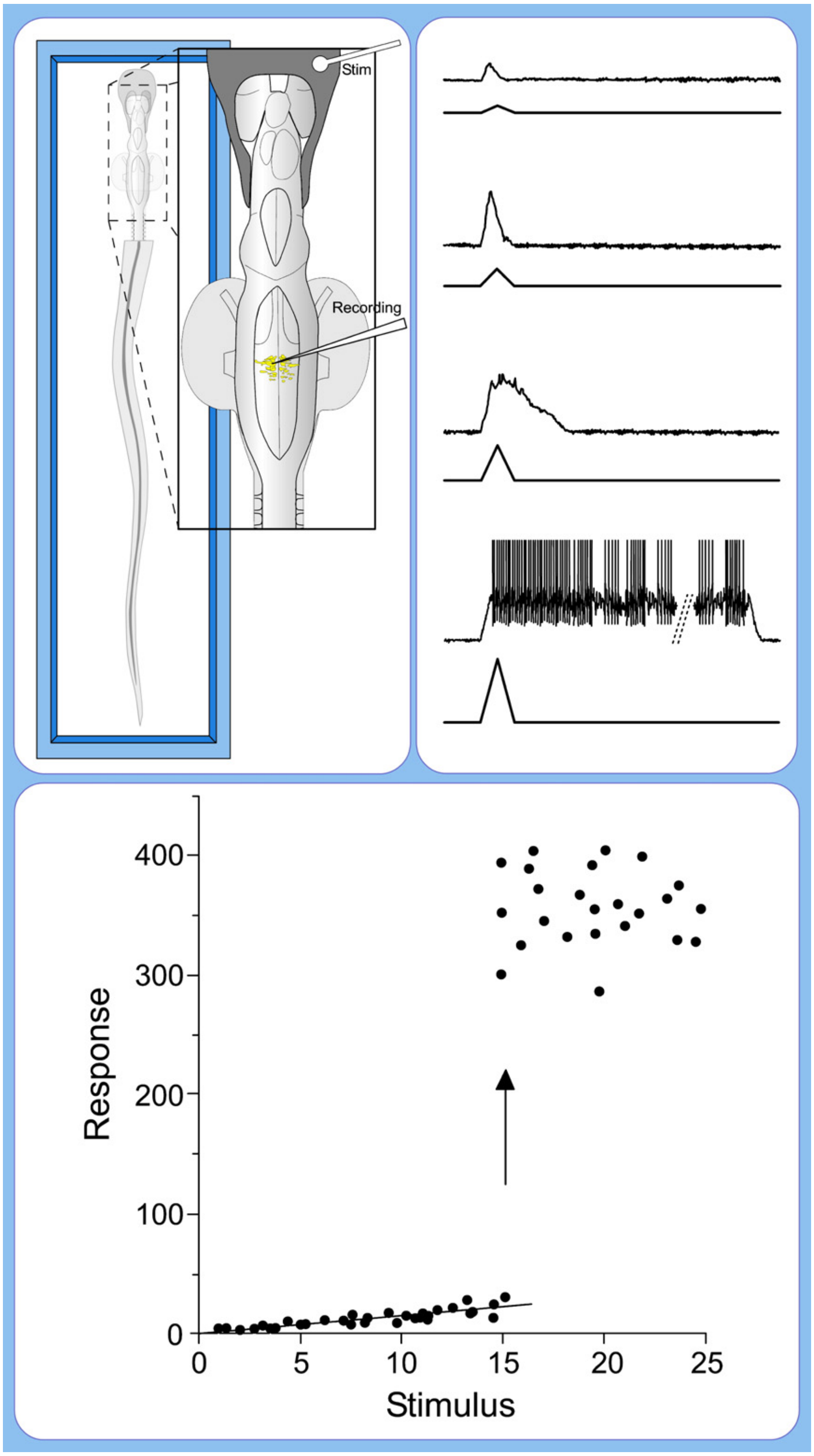

Fig. 2 – Responses of reticulospinal cells to mechanical skin stimulation. Top left: the semi-intact preparation in which mechanical pressure is applied to the skin. The responses are recorded intracellularly in reticulospinal cells. Right: the synaptic responses (top trace) match perfectly well with the pressure applied to this skin, until a threshold level is reached, at which sustained depolarizations are elicited with superimposed spiking activity (bottom pair of traces) activating the spinal locomotor networks. Bottom: relationship between the size of the response and strength of the stimulus. Note that there is a very close linear correlation between the response and stimulus at low intensities; the linearity breaks down at higher intensities. The figure was computer redrawn from original physiological recordings illustrated in Viana Di Prisco et al. (2000).

region is conveyed by trigeminal primary afferents with cell bodies located in the trigeminal ganglion, except for some located within the rhombencephalon and rostral spinal cord (Finger and Rovainen, 1982). The central projections of these sensory afferents course within the lateral part of the rhombencephalon in a region referred to as the alar plate (Northcutt, 1979; Koyama et al., 1987). Anatomical and physiological studies indicate that the trigeminal relay neurons are distributed throughout the rostrocaudal extent of the alar plate, in the nucleus of the descending root of the trigeminal nerve, most probably equivalent to the principal and spinal trigeminal nuclei in mammals (Viana Di Prisco et al., 1995, 2005). The use of a semi-intact preparation preserving parts of the skin with the entire CNS isolated *in vitro* has allowed us to examine the responses elicited in reticulospinal cells by mechanical stimulation of the skin (Fig. 2, top left). There was a stunning match between the size of the force exerted on the skin and the elicited response in reticulospinal cells (Fig. 2, bottom; Viana Di Prisco et al., 1997, 2000). As the pressure applied to the skin increased, so did the synaptic responses in reticulospinal cells (Fig. 2, top left). This occurred until a threshold level was reached at which the synaptic responses became very large and were sustained for long periods of time in reticulospinal cells. The sustained depolarizations were then accompanied by superimposed action potentials (Fig. 2).

To examine the behavioral effects of such sustained discharges, we used a semi-intact preparation where the brain and rostral spinal cord were dissected free from most of the surrounding muscle tissue and skin, preserving only a patch of skin over the dorsal aspect of the head. In addition, the caudal two thirds of the body were kept intact and allowed to freely swim in the recording chamber. As the mechanical skin stimulation reached the aforementioned threshold level, the elicited sustained depolarizations in reticulospinal neurons were accompanied by locomotor movements of the body (Viana Di Prisco et al., 1997), suggesting that the sustained activity in brainstem reticulospinal cells provides the sufficient excitation to the spinal locomotor networks to generate a sustained bout of swimming. We took advantage of this *in vitro* semi-intact preparation to examine the cellular mechanisms that are involved in transforming a sensory input into a

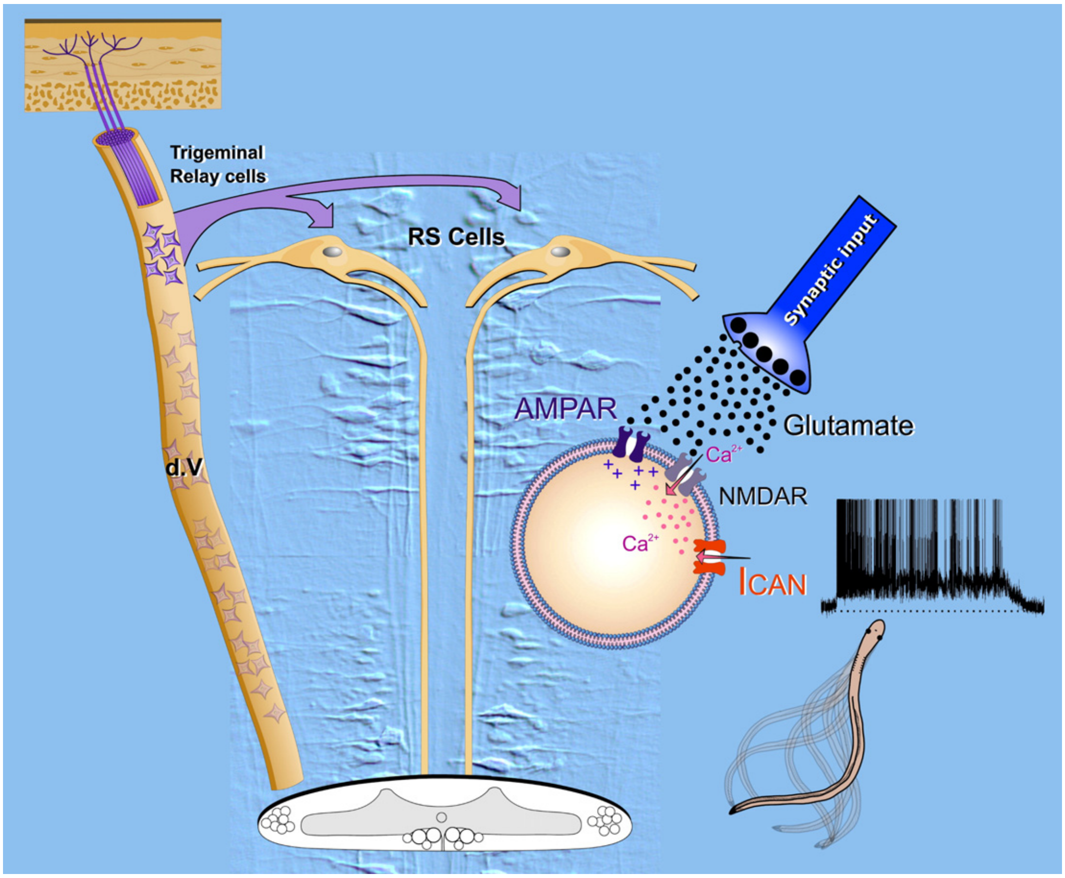

Fig. 3 – Schematic drawing illustrating the proposed mechanism by which a short-lasting sensory signal is transformed into a long-lasting motor command in reticulospinal cells to elicit locomotion. Mechanical stimulation of the skin over the head region generates discharges in primary afferent fibers traveling in the trigeminal nerve. The central projections of the afferents reach relay cells located in the descending root of the trigeminal nerve (d.V) that in turn project to reticulospinal cells (RS cells). The sustained depolarizations generated in reticulospinal cells after strong mechanical skin stimulation require the activation of NMDA receptors (NMDAR), which bring about a rise in intracellular Ca^{2+}. It is proposed that the entry of Ca^{2+} in the cell activates a Ca^{2+}-activated non-selective cationic conductance (I_{CAN}) believed to be crucial for the sustained depolarizations in the reticulospinal cells.

brainstem sustained locomotor command. It was found that the sustained depolarizations elicited by strong mechanical stimulation required the activation of NMDA receptors (Viana Di Prisco et al., 1997). Moreover, the sustained depolarizations were accompanied by a sustained rise in intracellular calcium concentration measured using calcium imaging. The rise in intracellular calcium levels also requires the activation of NMDA receptors. Whether the rise in calcium levels and the sustained depolarizations had any causal relationship was examined. The responses to strong sensory stimulation were characterized in reticulospinal cells before and after intracellularly injecting the calcium chelator, BAPTA, into the recorded reticulospinal cell. The calcium chelator was injected into a single reticulospinal cell and had no effect on synaptic transmission. After BAPTA, the sustained depolarizations could no longer be elicited in the recorded cell even upon strong sensory stimulation indicating that the depolarizations require calcium and rely on intrinsic mechanisms of reticulospinal cells (Viana Di Prisco et al., 2000). A likely conductance candidate underlying the sustained depolarizations was a calcium activated non-selective cationic conductance (I_{CAN}). Flufenamic acid, which is known to block I_{CAN}, was applied locally over the intracellularly recorded reticulospinal cell and abolished the sustained depolarizations in response to strong sensory inputs. These results support the hypothesis that I_{CAN} is involved in generating the sustained depolarizations by contributing to the rise of calcium levels in the cell in response to the activation of NMDA receptors (Fig. 3). Experiments are underway to examine other potential sources of calcium that may be involved in the sustained depolarizations as well as the mechanisms that could stop them. Intrinsic membrane properties could play a role, but because pairs of reticulospinal cells on the two sides show identical patterns of depolarization, common inputs are likely to be involved in repolarizing the cells. We are now pursuing this in further detail (Fénelon, Antri, Dubuc, unpublished observations).

Other sensory inputs have been shown to elicit locomotor activity in lampreys. For instance, activation of the lateral line system, which includes photoreceptors distributed in the skin of the tail, can induce bouts of locomotion. Unilateral illumination of the tail elicited an initial turn followed by rectilinear swimming (Deliagina et al., 1995). Lateral line afferents project bilaterally (Ronan, 1988). Lampreys are also sensitive to weak, low-frequency electric fields and it was shown that lateral line afferents are involved (Fritzsch et al., 1984; Kishida et al., 1988; Chung-Davidson et al., 2004). Electrical fields also generate responses within the hindbrain and midbrain, in the torus semicircularis and the optic tectum (Bodznick and Northcutt, 1981). Although the exact nature of the behavior elicited or the cellular mechanisms involved has not been established, it is likely that the lateral line system can play a significant role in the initiation of locomotion in lampreys. Startle reactions are also elicited in response to vibrations (Currie, 1991; Currie and Carlsen, 1985, 1987a,b, 1988) and they disappear after a labyrinthtectomy.

The visual system is well developed in adult lampreys. Stimulation of the optic nerve on one side elicits strong depolarizations in ipsilateral reticulospinal cells (Ullén et al., 1997). These responses have been shown to play a crucial role in postural control in lampreys. It was found that the optic nerve responses were relayed in the contralateral pretectum by large cells sending their axons to contralateral reticulospinal cells, indicating that retinal inputs are crossing twice before reaching reticulospinal cells (Zompa and Dubuc, 1996). More recently, there has been compelling evidence that stimulation of the optic tectum elicits locomotion in combination to eye movements and postural adjustments (Saitoh et al., 2004). Stimulation of different areas of the tectum was carried out in head-restrained semi-intact lampreys. Eye movements were evoked in different directions depending on site of stimulation. Locomotion was also elicited with locomotor-related eye movements in response to stimulation of the caudo-medial tectum or without eye movements when the rostro-lateral tectum was stimulated. The movements of the eyes and trunk following the stimulation of the tectum were strictly coordinated, and a spinal cord lesion did not impair eye movements, suggesting that the latter do not result from feedback from the spinal cord locomotor networks.

We recently investigated the possibility that the olfactory inputs could elicit locomotor activity. Chemical stimulation of the sensory neurons within the olfactory epithelium elicits strong depolarization in reticulospinal neurons. Electrical stimulation of the olfactory nerve produces similar effects. The long latencies suggest that several synapses are present in this neuronal pathway to reticulospinal cells. Locally injecting glutamate in one olfactory bulb elicits bouts of fictive locomotion in a preparation where the first 10 to 15 spinal segments are kept intact (Derjean, St-Pierre, Auclair, Zielinski and Dubuc, unpublished observation). Experiments are underway to identify the pathways by which olfactory inputs activate the brainstem reticulospinal command neurons to eventually elicit locomotion.

4. Locomotor centers in the brain of lampreys

In addition to directly resulting from the activation of sensory inputs, locomotion can be triggered by internal cues as mentioned above. It is believed that locomotor centers within the forebrain and brainstem play a crucial role in such goal-directed locomotion. The cellular mechanisms underlying the neural control of locomotion in this context have not been established yet in any vertebrate species. In the early 1960s, a localized region at the border between the mesencephalon and the pons was shown to generate locomotion in cats walking over a treadmill. This brainstem region was named mesencephalic locomotor region (MLR). Electrical stimulation of this region elicited graded locomotor output such that, at low stimulation intensity, locomotion was characterized by slow walking and, as stimulation intensity increased, the animals trotted and then galloped (Shik et al., 1966). It was later demonstrated that the MLR did not project directly to the spinal cord, but the effects were relayed by reticulospinal cells before reaching the spinal locomotor networks to elicit locomotion (for a review, see Jordan, 1998). The MLR was later described in several other animal species and found to be located in the same region within the brainstem (for a review, see Grillner et al., 1997). Whether the animals would walk, fly, or swim, locomotion was elicited in a graded fashion. The possibility that the same brainstem region could control two modes of locomotion in the same animals was investigated in the adult salamander, a lower vertebrate displaying both swimming and terrestrial stepping. The two locomotor modes differ as to their patterns of activation of epaxial musculature (intersegmental coordination pattern) and limb muscles (Frolich and Biewener, 1992; Delvolvé et al., 1997). Salamanders were shown to possess an MLR also located at the mesopontine border (Cabelguen et al., 2003). Moreover, the two modes of locomotion exhibited by salamanders (i.e. stepping and swimming) could be evoked by electrical microstimulation of the MLR in a semi-intact preparation where the body and the posterior limbs were kept intact. At threshold current strength, rhythmic limb movements and intersegmental coordination were induced such as during stepping. As the stimulation strength was subsequently increased, the frequency of stepping became more rapid until the limbs were eventually held back against the body wall and swimming movements of the trunk were induced. A further increase of the stimulation strength induced an increase of the frequency and amplitude of the swimming movements. These results show that salamanders do possess an MLR that controls two distinct patterns of locomotion (stepping and swimming) depending on its activation strength.

In mammals, the MLR was shown to receive inputs from the basal ganglia. For instance, stimulation of nucleus accumbens elicits locomotion that is abolished by inactivation of the MLR (Brudzynski and Mogenson, 1985). Projections from nucleus accumbens to the MLR, relayed by the ventral pallidum, are involved. It was proposed that pallidum neurons are tonically active, keeping the MLR under tonic inhibition. The activation of locomotion by the basal ganglia would then result from a disinhibition of the MLR, leading to the activation of reticulospinal neurons (for a review, see Grillner et al., 1997). Consistent with this view is the observation that injections of a $\mathrm{GABA_A}$ receptor antagonist into the MLR of mammals elicit locomotion (Garcia-Rill et al., 1990). Other areas are known to project to the MLR and thus could be involved in the initiation of locomotion. It was proposed that the MLR consists of different parts involved in triggering locomotion in relation to different behavioral contexts (Sinnamon, 1993; for a review, see Jordan, 1998).

The MLR was originally discovered in mammals and we have shown that it is present in lampreys (Sirota et al., 2000). Electrical stimulation of a region located at the mesopontine border initiates swimming in a semi-intact lamprey preparation. The power of swimming, expressed by the strength of the muscle contractions and the frequency and amplitude of the lateral displacement of the body or tail, increased as the intensity or frequency of the stimulating current was increased. The MLR is thus conserved throughout vertebrate phylogeny in a localized brainstem region that produces muscle synergies underlying swimming in cyclostomes and fish, stepping in tetrapods, and flying in birds. This is true despite differences in locomotor appendages in these animal species.

We have reviewed above the importance of the reticulospinal system in initiating and controlling locomotor activity in lampreys. In mammals, stimulation of the MLR activates the spinal pattern generators through a monosynaptic activation of reticulospinal cells in the pons and medulla oblongata (Steeves and Jordan, 1984, for reviews, see Jordan, 1986; Grillner et al., 1997). The mechanisms by which this is done are still unknown in mammals. We have begun a series of experiments to unravel such mechanisms in lampreys (Le Ray et al., 2003). We demonstrated a significant contribution of cholinergic inputs to reticulospinal neurons from the MLR. Moreover, a local application of either acetylcholine or nicotine produces a direct dose-dependent excitation in reticulospinal neurons and induces active or fictive locomotion. It also accelerates ongoing fictive locomotion. Choline acetyltransferase-immunoreactive cells are found in the region identified as the MLR of lampreys and nicotinic antagonists depress, whereas physostigmine enhances the compound EPSP evoked in reticulospinal neurons by electrical stimulation of the MLR. In addition, cholinergic inputs from the MLR to reticulospinal neurons are monosynaptic. When the brainstem is perfused with the nicotinic antagonist D-tubocurarine, the induction of swimming by MLR stimulation is depressed, but not prevented, in a semi-intact preparation. Therefore, cholinergic inputs from the MLR to reticulospinal cells play a substantial role in the initiation and the control of locomotion in lampreys.

One of the key questions relative to the role of the MLR in controlling the intensity of locomotion concerns the recruitment pattern of reticulospinal cells by the MLR. One possibility is that additional reticulospinal cells are recruited as the intensity of stimulation increases. Alternatively, all reticulospinal cells could be recruited at low stimulation intensity and their level of excitation would increase progressively to generate a more powerful descending command to spinal cord locomotor networks. These two hypotheses are obviously not mutually exclusive. We have recently examined the relative contribution of the middle (MRRN) and the posterior (PRRN) rhombencephalic reticular nuclei to swimming controlled by the MLR (Brocard and Dubuc, 2003). Intracellular recordings were performed to examine the inputs from the MLR to reticulospinal neurons. Stimulation of the MLR elicited monosynaptic excitatory responses of a higher magnitude in the MRRN than in the PRRN. This differential effect was not attributed to intrinsic properties of reticulospinal neurons. Paired recordings showed that, at threshold intensity for swimming, spiking activity was primarily elicited in reticulospinal cells of the MRRN. Interestingly, cells of the PRRN began to discharge at higher stimulation intensity only when MRRN cells had reached their maximal discharge rate. Glutamate antagonists were ejected in either nucleus to reduce their activity. Ejections over the MRRN increased the stimulation threshold for evoking locomotion and resulted in a marked decrease in the swimming frequency and the strength of the muscle contractions. Ejections over the PRRN decreased the frequency of swimming. These results support a sequential recruitment of the two groups of reticulospinal cells during MLR-induced locomotion. Reticulospinal cells in the MRRN are primarily involved in initiation and maintenance of low-intensity swimming. At higher frequency locomotor rhythm, reticulospinal cells in both the MRRN and the PRRN are recruited (Fig. 4).

Unilateral activation of the mesencephalic locomotor region has been shown to produce symmetrical bilateral locomotion in all animal species tested to date. How this

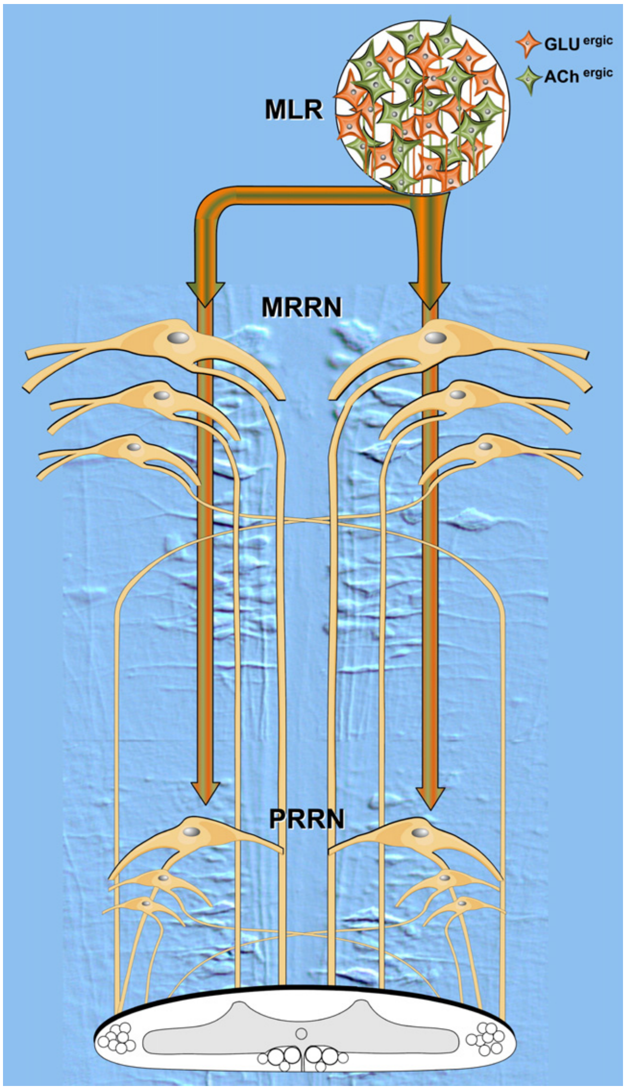

Fig. 4 – Schematic drawing representing the connections between the MLR and reticulospinal cells in the middle (MRRN) and posterior (PRRN) rhombencephalic reticular nuclei. The MLR sends monosynaptic cholinergic and glutamatergic projections to reticulospinal cells. The projections are symmetrical on both sides. At a low stimulation intensity, the MLR activates reticulospinal cells in the MRRN and, as the stimulation strength increases, reticulospinal cells in the PRRN become activated.

occurs has remained unresolved. In cats and rats, reticulospinal neurons were shown to receive inputs from the MLR on both sides (Orlovsky, 1970; Garcia-Rill and Skinner, 1987). The symmetry of the inputs, however, could not be established in these experiments. We have reexamined the possibility that symmetrical locomotion induced by a unilateral stimulation of the MLR could result from symmetrical bilateral inputs onto reticulospinal cells from the MLR on one side in lampreys (Brocard, Hatem, Fénelon, and Dubuc; unpublished observations). Paired intracellular recordings of homologous reticulospinal cells on both sides were performed and their responses to electrical stimulation of the MLR on one side were examined in semi-intact preparations. Highly similar excitatory postsynaptic potentials at fixed latency were elicited in homologous reticulospinal cells on both sides. The threshold intensity was the same in homologous reticulospinal cells on both sides and symmetrical increases in the magnitude of bilateral responses occurred as the stimulation intensity of the MLR was increased. Microinjection of AMPA into the MLR also elicited symmetrical recruitment on both sides. Intracellular recordings are biased towards the larger cells. Calcium imaging experiments confirmed the bilateral activation of smaller reticulospinal cells as well. In a Ringer's solution containing a high concentration of divalent cations, the synaptic responses elicited in homologous reticulospinal cells persisted and maintained a constant latency during high frequency stimulation, suggesting that the MLR projects monosynaptically to reticulospinal cells on both sides and provides symmetrical inputs to them. During locomotion in the semi-intact preparation, the discharge pattern was also very similar in homologous bilateral reticulospinal cells. Taken together these results suggest that the symmetry of the MLR command is organized at the brainstem level.

We also investigated the possibility that muscarinic receptors might be involved in the control of locomotion. We found that muscarinic drugs powerfully modulated sensory transmission to reticulospinal cells. When muscarinic agonists or antagonists were locally applied either directly over reticulospinal cells or within the trigeminal relay area, sensory transmission was respectively depressed or potentiated (Le Ray et al., 2004). The source of this modulation is likely to be the MLR because sustained stimulation of the MLR depresses trigeminal input transmission to reticulospinal cells (Boutin, Fénelon, Diallo, and Dubuc; unpublished observations). It is also noteworthy that bath applications of muscarinic agonists induce sustained recurrent depolarizations in reticulospinal cells. The effects are not produced by a direct activation of reticulospinal but through a pre-reticular effect (Smetana et al., 2007). We have identified a group of cells located in the lateral basal plate at the level of the rostral pole of the PRRN, which display immunoreactivity to muscarinic receptors and are likely candidates involved in the generation of the observed depolarizations after bath application of muscarinic agonists. We have also preliminary evidence that these neurons are activated by the MLR. Functionally, such activation could provide an extra boost of excitation to reticulospinal neurons in order to increase the descending locomotor command and increase the power of swimming.

One important question relates to the neural networks involved in controlling MLR activity. To address this, we have begun anatomical and physiological studies to identify possible inputs to the MLR. Substance P initiates locomotion when injected in the brainstem of mammals. Injection of substance P in the MLR of lampreys elicits bouts of locomotion (Brocard et al., 2005). When substance P is injected in the MLR the current threshold needed to induce locomotion by MLR stimulation is decreased, and the size of the postsynaptic responses of reticulospinal cells to MLR stimulation is concomitantly increased. There is also a significant tachykinergic innervation in lampreys (Auclair et al., 2004). In collaboration with the group of Sten Grillner, we have found that injections of the GABA antagonist, gabazine, in the MLR also elicit bouts of locomotion in a semi-intact preparation, suggesting that the MLR of lampreys is also under tonic inhibitory control (Ménard et al., 2007) as mentioned above for the mammalian system. These physiological results suggest the presence of GABAergic neuron projections to the MLR of lampreys. To test this, we examined anatomical projections to the MLR in combination with immunohistochemistry for GABA. Double-labeled neurons were found in several forebrain areas including the basal ganglia (Ménard et al., 2007). The exact source of GABAergic inhibitory control of the MLR remains to be established using electrophysiological experiments.

Many other regions of the brain can be stimulated to elicit locomotion, such as the olfactory bulb, optic tectum, or trigeminal sensory nucleus to name a few. However, not all of these regions can elicit locomotor activity with graded intensity in response to increasing levels of stimulation (see above). Although what defines a locomotor center has not been strictly established in the literature, it is tempting to propose that a locomotor center would be a region of the CNS initiating locomotor activity and controlling its intensity in a graded fashion. One other region that fits these criteria in lampreys is an area in the diencephalon that was identified by the group of Sten Grillner (El Manira et al., 1997). It was named diencephalic locomotor region (DLR). Located in the ventral thalamus, the DLR sends direct projections to reticulospinal neurons in the rhombencephalon. It initiates locomotion via this connection. The physiological projection from the DLR to reticulospinal cells involved mainly monosynaptic glutamatergic projections. Stimulation of the DLR produces rhythmic firing of reticulospinal neurons and elicits rhythmic bursts of activity in the spinal ventral roots. The projections to the DLR were also investigated and they were found to originate from the olfactory bulb, pallial areas, striatum, preoptic nucleus, hypothalamus, dorsal thalamus, optic tectum, and dorsal isthmic gray. The recruitment pattern of reticulospinal neurons in response to DLR stimulation has not been established yet, nor do we know the exact behavioral contexts in which either the MLR or DLR is being recruited. Chemical stimulation of other areas in the brain of lampreys can generate locomotor activity in larval lampreys (Paggett et al., 2004). The authors showed that an area seemingly located in the thalamus (see DLR above) could be stimulated to elicit fictive locomotion. Another region in the rostrolateral rhombencephalon was also identified as eliciting fictive locomotion. Interestingly, blocking activity in more rostral areas prevented locomotion from being elicited from this region, suggesting that it elicits locomotion through ascending projections to other areas involved in locomotion. The projections to and from these areas would need to be established in order to clarify their role in locomotion.

In this paper, we have reviewed recent findings relative to the initiation of locomotion in lampreys. In these animals, locomotion can be initiated in response to external sensory cues as well as by internal inputs associated with specific biological needs. Sensory-evoked swimming relies on a rather simple circuitry with few connections between the sensory neurons and reticulospinal cells which act as command neurons in the brainstem. Specific membrane properties of reticulospinal cells were shown to be responsible for the transformation of short-lasting sensory signals into a sustained motor command. Goal-directed locomotion associated with internal motivation relies on more complex connections within the brainstem and the forebrain. At present, two locomotor centers were identified. They project directly to reticulospinal neurons and are likely to play a significant role in goal-directed locomotion.

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