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Neural networks that co-ordinate locomotion and body orientation in lamprey

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The networks of the brainstem and spinal cord that co-ordinate locomotion and body orientation in lamprey are described. The cycle-to-cycle pattern generation of these networks is produced by interacting glutamatergic and glycinergic neurones, with NMDA receptor–channels playing an important role at lower rates of locomotion. The fine tuning of the networks produced by 5-HT, dopamine and GABA systems involves a modulation of Ca^{2+}-dependent K^+ channels, high- and low-threshold voltage-activated Ca^{2+} channels and presynaptic inhibitory mechanisms. Mathematical modelling has been used to explore the capacity of these biological networks. The vestibular control of body orientation during swimming is exerted via reticulospinal neurones located in different reticular nuclei. These neurones become activated maximally at different angles of tilt.

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THE NERVOUS SYSTEM can be studied at many different levels from ion channels, single cells and synapses to neural networks and global cognitive functions. Individual neural networks represent an important category of functional modules that are at an intermediary level of complexity in the nervous system. Different specialized networks are used in sensory systems, as well as in the co-ordination of a host of different movement patterns from swallowing to skilled movements. One of the most complex movement patterns that any nervous system can co-ordinate, and recruit at will, is that producing

locomotion. In a mammal, hundreds of muscles are involved, each of which is activated during a particular phase of the movement cycle. In all vertebrates, the co-ordination of these muscles is produced by spinal networks that are referred to as central pattern generators[1,2] (CPGs). The level of activity of these CPGs is controlled from reticulospinal neurones, which project from the lower brainstem to the spinal cord. The higher the level of activity in these reticulospinal neurones, the faster the animal will locomote. This type of general organization, that also includes sensory modulation, applies to all vertebrates from fish to tetrapods, such as reptiles and mammals (including primates). If the nervous system is to be understood in a mechanistic perspective, these networks must be understood in terms of interacting nerve cells, transmitters and membrane properties. This requires an experimental situation that permits an analysis at the cellular level. So far, a detailed analysis, both at the cellular and network levels, has been carried out in simple vertebrate models[3–5] (lamprey and tadpole) only, while the mammalian brainstem and spinal cord has as yet proved too complex. However, the neonatal *in vitro* preparation from the rat, and the different *in vivo* preparations (for example, cat) continue to provide important new insights[6–8].

The lamprey originates from a group of animals that diverged from the main vertebrate evolutionary line at a stage when ordinary fish had not yet appeared, that is, around 450 million years ago. The lamprey has, however, changed to a comparatively small degree and, in some sense, it can be regarded as a prototype vertebrate. It has a brainstem and spinal cord with all basic vertebrate features, but with orders of magnitude fewer nerve cells of each type than higher vertebrates. Moreover, its brainstem and spinal cord can be maintained *in vitro* over a period of several days, with spontaneous or induced activity in the locomotor CPGs (Fig. 1). These conditions are favourable from an experimental point of view, and have enabled us to detail the networks that underlie the locomotor behaviour in cellular terms[3,9,10].

The lamprey swims by producing an alternating activation of motoneurones on the left and the right side of each segment along the body. In addition, the 100 different segments are activated successively with a phase delay. This results in the propagation of an undulatory muscular wave in a direction from rostral to caudal. This phase delay is around 1% of the cycle duration[11,12] (Fig. 1A). This caudally directed undulatory wave pushes the animal forward through the water. The higher the frequency of alternation, the faster it will swim. The speed of the undulatory wave will, as a consequence of the constant phase delay, be proportional to the frequency of alternation[3]. While swimming, the animal generally maintains the dorsal side up, and if this position is disturbed, it will be corrected rapidly, mainly as a result of signals from the vestibular apparatus[13]. These signals act on reticulospinal neurones, which project to the spinal cord.

The locomotor network in the brainstem and spinal cord

Brainstem neurones are thus responsible for the initiation of locomotion, while the spinal cord

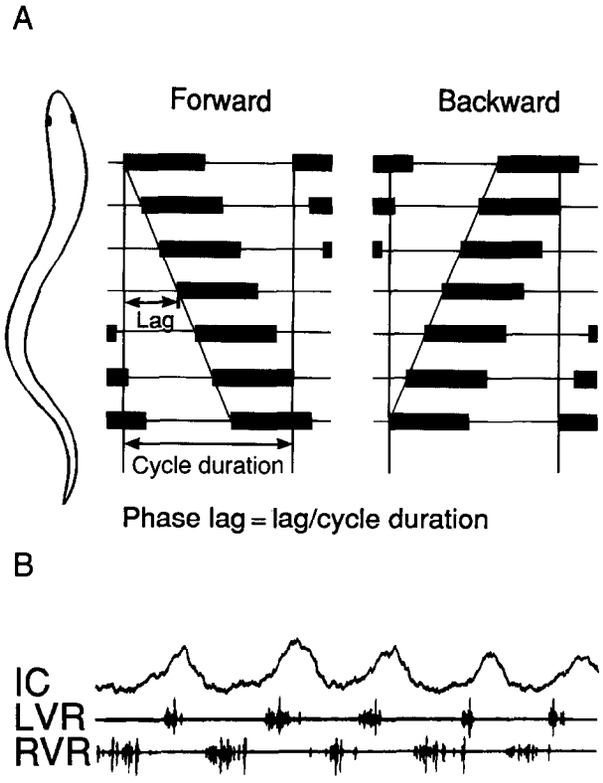


Fig. 1. ***Schematic representation of the motor pattern of the lamprey during swimming, and fictive locomotor activity of the preparation of the spinal cord*** **in vitro.** **(A)** *Locomotor synergy. To the left, a lamprey is represented with the characteristic undulatory body shape. The undulatory wave is propagated towards the tail during forward swimming. The graph to the left shows the motor pattern of the segments along the body during forward swimming. The electromyographical activity is delayed from segment to segment; this lag is always a certain proportion of the cycle duration, regardless of whether the cycle duration is 2 s or 0.1 s (around 1% of the cycle duration per segment). To the right in* A, *the motor co-ordination during backward swimming is shown in which the phase coupling is reversed.* **(B)** *Recordings of fictive locomotor activity in the* in vitro *preparation of the isolated lamprey spinal cord. The motor activity can be elicited by bath application of excitatory amino acids (EAA), such as NMDA-receptor agonists, and can be recorded extracellularly from the ventral roots on the left (LVR) and right (RVR) sides. There is a strict alternation of bursts between the two sides of the segment. The trace above the ventral-root recordings is an intracellular (IC) recording from a moto neurone on the left side.*

provides the motor pattern. The lamprey spinal cord can be divided into small pieces (two to three segments), each of which can generate alternating burst activity, demonstrating a distributed capacity for pattern generation along the entire spinal cord.

Initiation

Glutamatergic reticulospinal neurones from the posterior and middle rhombencephalic nuclei project to the spinal cord (Fig. 2A), and activate motoneurones and interneurones[15,16] that belong to the network, and can thereby elicit locomotor activity. The reticulospinal neurones can be activated from rostral brainstem structures and by a variety of sensory stimuli, including the lateral line nerve, which carries different types of information from the body surface. These reticulospinal cells activate both AMPA/kainate and NMDA receptors on the spinal cells of the locomotor CPGs. The spinal network, in isolation, can also be turned on by a general increase in excitability, such as an activation of glutamate

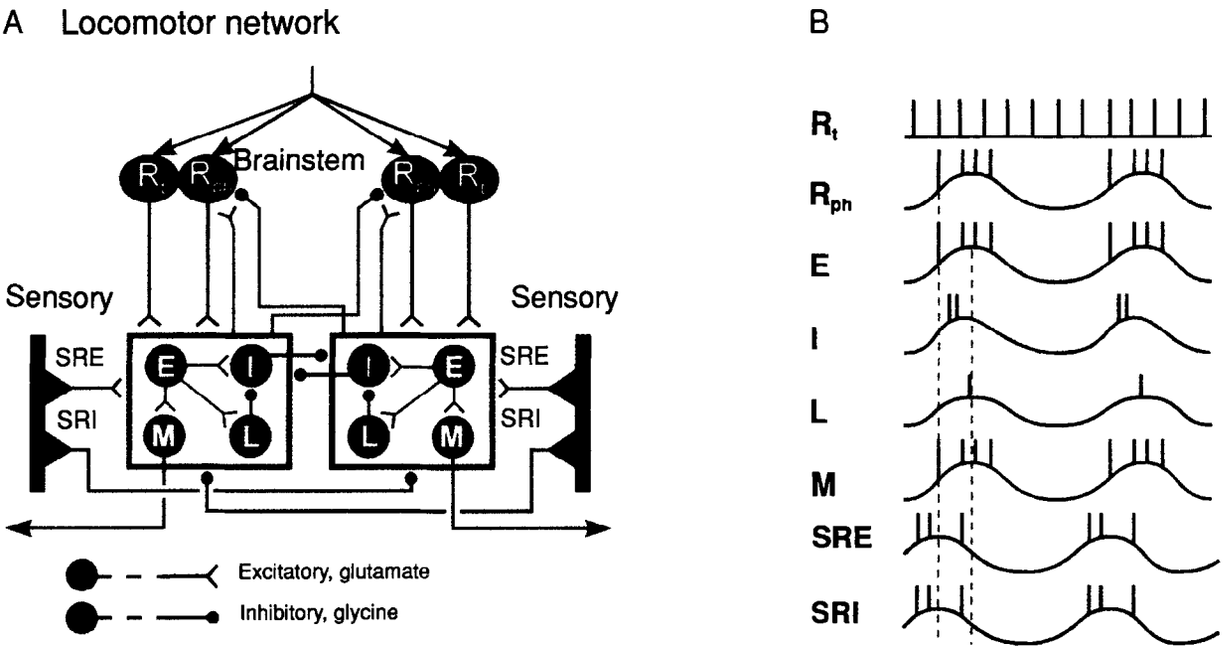


Fig. 2. ***The segmental neuronal network that co-ordinates locomotion.*** **(A)** *A schematic representation of the brainstem, segmental and sensory components of the neural system that generate burst activity. All neurone symbols denote populations of neurones rather than single cells. The reticulospinal glutamatergic brainstem neurones [phasic (R_{ph}) and tonic (R_t)] project to the spinal cord, and excite all the spinal neurones that are depicted within the black box. The excitatory interneurones (E) excite all types of spinal neurones within the box, that is, inhibitory glycinergic interneurones (I) that cross the midline and inhibit all neurones within the contralateral box, the lateral interneurone (L), which inhibits the I interneurone, and motoneurones (M), which are cholinergic. The stretch-receptor neurones are of an excitatory (SRE) type that excites neurones within the ipsilateral box and an inhibitory (SRI) type that inhibits all neurones within the contralateral box. Inhibitory and excitatory neurones are represented in blue and red, respectively. Synapses that are shown to terminate on the frame of the box indicate effects that are common to all neurones within the box. The excitatory and inhibitory effects from the spinal neurones (box) back to the phasic neurones are indicated as monosynaptic but might have additional relay interneurones. The tonic neurones receive no feedback from the spinal cord. Note that only one cell of each type is indicated in the scheme although each cell represents a group of cells.* **(B)** *A schematic representation of the activity patterns of the different nerve cells considered in A, and their time relations. Activity on one side only is shown for clarity. Note that the spinal-nerve cells are approximately in phase but that the activity of the I-interneurones terminates before that of E; this termination might be partially a result of L-interneurone activity but could also relate to intrinsic properties of I-interneurones (compare with Ref. 14).*

receptors by superfusion of the preparation by glutamate-receptor agonists (Fig. 1B). Activation of NMDA receptors can thus give rise to an alternating burst activity in a low-frequency range (0.1–3 Hz), while a selective AMPA/kainate-receptor drive provides a burst rate from around 1–8 Hz (Refs 3 and 17–19).

The spinal segmental CPG with sensory control

The spinal network (Fig. 2A) contains excitatory (E) glutamate interneurones that project to all types of ipsilateral interneurones and to motoneurones[20] (M), and inhibitory (I) glycinergic interneurones with a crossed axonal process that inhibit all types of cells in the locomotor network on the contralateral side[21]. In addition, there are excitatory and inhibitory sensory stretch-receptor neurones (SRE and SRI, respectively) that sense the lateral-bending movements occurring during locomotion, and act on the CPG neurones[22,23].

Figure 2A shows the basic components of the segmental burst-generating network, with the reticulospinal system for initiation [phasic (R_{ph}) and tonic (R_t)], and the sensory stretch-activated receptors. Can this circuitry account for the segmental burst generation over the entire physiological range? We think it can: the evidence is summarized below and in Box 1. Let us first consider a simple case in which the excitability of all cells in the spinal network is increased (for example, by perfusion of agonists of glutamate receptors), such that the cells will tend to fire action potentials when they are not inhibited (Fig. 2B). In this case, if one half of the network is active (the nerve cells contained within one box, see Fig. 2A), the other half will become inhibited by I-interneurones, and a continuous asymmetric activity would occur, provided that there were no mechanisms to terminate the ongoing activity. However, there are several such mechanisms on the circuit and sensory level but most important are perhaps the cellular properties of the cells in the network[24] (for example, spike-frequency adaptation and plateau potentials, as described in Box 1). In the isolated spinal cord, the burst termination can be accounted for by these different factors. K_{Ca} channels appear to play a crucial role in slow swimming[24] but at higher rates other factors become more important, as deduced from experiments in which the action of K_{Ca} channels has been blocked partially.

During normal swimming, the intraspinal stretch receptors[22,23], which sense the locomotor movements, also contribute to the burst termination in the following way (compare with Figs 2A and 3). The active side of a segment will cause muscle contraction and a shortening, which will extend the contralateral side and its stretch-receptor neurones, localized along the lateral margin of the spinal cord[22] (compare with Fig. 3B). These stretch receptors are of two kinds, one that inhibits (SRI) the contralateral active side, and another that provides additional excitation (SRE) to network interneurones that are ipsilateral to the stretch receptors (Fig. 3B). The latter

side of the network is, at this point of the movement cycle, on the verge of becoming active[3,23,25]. Indeed the sensory movement-related input is powerful enough to entrain the CPG to slow down or speed up its burst activity (Fig. 3A)[26,27].

The initiation of a new burst is thus mostly a result of a disinhibition (Box 1), in combination with a background excitatory drive, which makes the E- and I-interneurones start to discharge. The E-interneurone will then further excite the I-interneurones and the motoneurones (Fig. 2). In addition, there are two voltage-dependent mechanisms that can boost the depolarization[28]: (1) the NMDA receptor–channels that are activated by glutamate will 'open up' only at more depolarized levels, and only then contribute efficiently to the depolarization; and (2) low-voltage activated Ca^{2+} channels that can be activated only on the rebound after a preceding inhibition. These two mechanisms contribute to a postinhibitory rebound excitation that assures that the burst will start. The I-interneurone will then effectively inhibit the contralateral side, which is of critical importance for maintaining a reciprocal burst activity.

The reticulospinal neurones provide an excitatory drive to the spinal cord to initiate burst activity and also a possible tonic drive. Some reticulospinal cells are active tonically, and others receive feedback from the spinal cord that results in a phasic modulation (Fig. 2A)[15,16,29,30]. These two signals provide the drive for locomotion.

Cellular analyses of biological networks require mathematical modelling

By applying an intuitive reasoning as above, a general feeling for which factors are important for the operation of the network can be obtained. This type of information can guide further experiments. However, to evaluate if all the experimental findings taken together really can account for the range of physiological activity of the network, mathematical modelling is required. Unfortunately, our brains cannot deal with this type of dynamic process, in which a number of factors are playing a role concurrently. In 1987, when we had understood some basic features of this spinal locomotor circuit, we started immediately to simulate the network[31] to test if the findings that we had obtained could account for relevant features of the rhythm generation[32–35]. Box 2 summarizes the 'realistic simulations' made of the different types of neurones in the network, and the pattern of network activity that was produced when the cells were connected in a manner similar to that demonstrated in Fig. 2, and also to the intersegmental co-ordination.

5-HT, dopamine, $GABA_B$ receptor, mGluR and peptidergic systems provide 'fine tuning' of the locomotor network

The phasic interaction in the pattern-generator system is thus produced by neurones that use glutamate and glycine as transmitters acting via ligand-operated ion channels. In addition, a number of slower G-protein-mediated modulators contribute to the fine tuning of the networks. For example, 5-HT and dopamine (DA) are co-stored in a midline system of spinal neurones, which form a dense

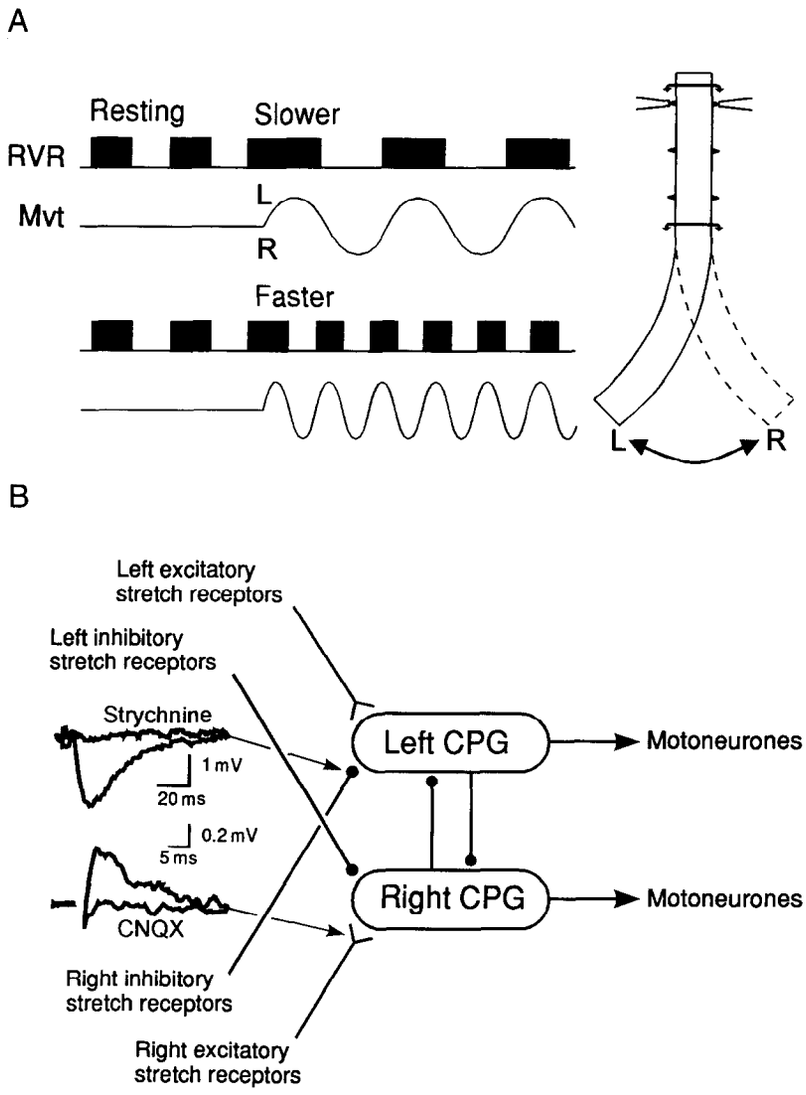


Fig. 3. ***The sensory control of the central motor pattern – entrainment and neural mechanisms.*** **(A)** *The effect of sensory, movement-induced input on the motor pattern that is produced by the isolated spinal cord. The resting motor pattern from one ventral root (RVR) is shown above, and lateral movement (Mvt), left (L) and right (R), mimicking swimming is applied to a spinal cord–notochord preparation (see drawing to the right in A). As movement is applied, the central motor pattern adapts to the superimposed movement, whether it is slower or faster than the resting burst rate, within a certain range.* **(B)** *The entrainment is a result of stretch-receptor neurones, which are located in the margin of the spinal cord, and which sense the lateral movements of the body (notochord). The stretch-receptor neurones are of two kinds. One type excites ipsilateral central pattern generator (CPG) interneurones and the other inhibits contralateral CPG neurones. To the left are shown postsynaptic potentials from a paired recording between a stretch-receptor neurone and a target neurone, demonstrating that the contralateral IPSP is glycinergic since it is blocked by strychnine, and that the ipsilateral EPSPs are glutamatergic since they are blocked by 6-cyano-7-nitroquinoxaline-1,2-dione[23] (CNQX).*

plexus[36,37]. It acts on the dendrites of the neurones of the locomotor network. 5-Hydroxytryptamine reduces conductance through the K_{Ca} channels, thus influencing both the post-spike slow afterhyperpolarization (sAHP) and the NMDA-mediated plateau (Fig. 4A). Thus, 5-HT will reduce summation of the sAHP which, everything else being equal, will create longer bursts, and delay the burst termination further (Box 1). It will also affect the intersegmental phase delay along the spinal cord. Functionally, this type of modulation might adapt the movements to an increased external resistance like strong water currents or during burrowing. Dopamine acts by a reduction of the Ca^{2+} currents via D_2 receptors and,

Box 1. Cellular factors that contribute to the control of burst duration

Ca^{2+}-dependent K^+ channels (K_{Ca}) play several roles in determining the moment of burst termination[a,b]. In each neurone, they are activated as a result of the Ca^{2+} entry during each action potential, and give rise to a long-lasting afterhyperpolarization (sAHP) that lasts around 0.1 s (see Fig. A solid line). Figure A illustrates the effect of changes of the amplitude of the sAHP. A neurone with a large sAHP will, at a moderate excitatory drive as in A, produce one action potential only. If the sAHP is reduced (pharmacologically, or by transmitter action), everything else being equal, the same neurone will instead produce three spikes during the identical excitatory drive. The adaptation of spike frequency depends on the summation of the sAHPs. If two or more spikes occur in succession, the sAHPs will summate, and a longer period of silence will follow. When this occurs in interneurones being part of the network on one side, the contralateral nerve cells will be relieved from inhibition (see Fig. 2, p. 272), and thus might, because of the background excitatory drive, have sufficient time to reach threshold and start firing. If so, they will inhibit the previously active side. In this way, the summation of sAHPs in network interneurones might suffice to generate burst termination and, by disinhibition, the onset of a contralateral burst.

Under activation of NMDA receptors, the cells in the network can also elicit a long-lasting, depolarizing plateau potential as a result of an activation of the voltage-dependent NMDA receptor–channels. Figure B shows an NMDA plateau potential and its dependence on K_{Ca} for termination. The rapid depolarization is caused by an opening of voltage-dependent NMDA receptor–channels, and the initial peak is caused by a balance between open NMDA receptor–channels and voltage-dependent K^+ channels. The NMDA receptor–channels also permit Ca^{2+} to pass through and accumulate inside the cell to activate K_{Ca} channels progressively, which are responsible for pulling the membrane potential down to a level at which voltage-dependent NMDA receptor–channels also start to close[a,c]. It is shown that after a depression of K_{Ca} by applying apamine, the plateau phase is prolonged markedly, demonstrating that K_{Ca} channels are important for terminating the plateau.

In cells that do not display NMDA plateau potentials, the activation of NMDA receptor–channels from, for example, exctitatory interneurones (Fig. 2) will lead to a continuous entry of Ca^{2+} throughout the burst, and a progressively increasing activation of K_{Ca}, which will gradually pull the membrane potential down, and decrease the chance of a further activation of the cells[c].

Similarly, K_{Ca} can be activated through the low-voltage activated (LVA) Ca^{2+} channels[d] that are opened as the cell is depolarized to a potential that is close to the threshold for the action potential.

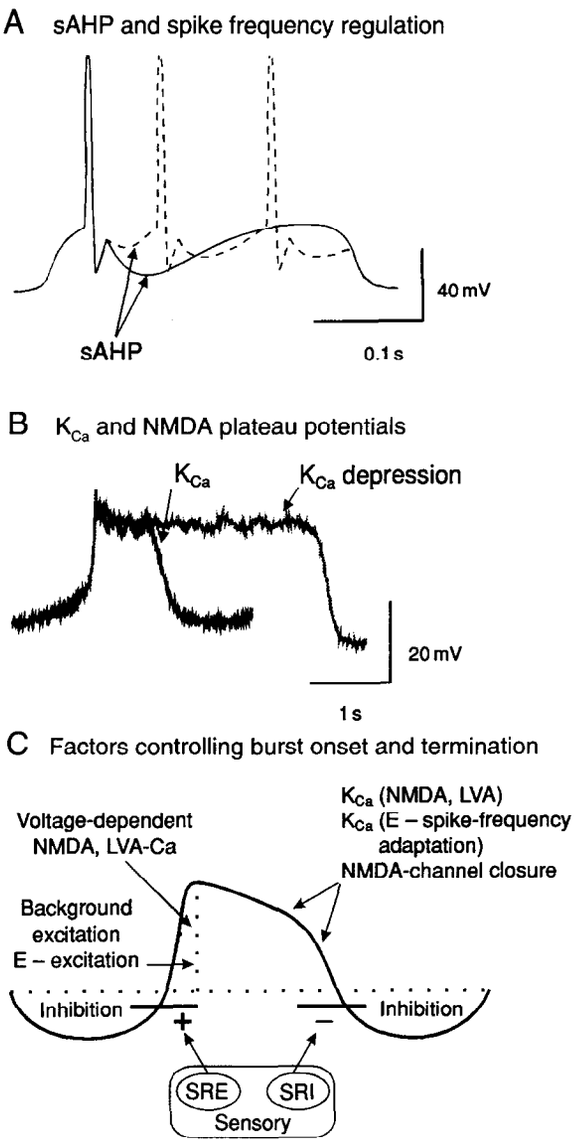
At faster rates of swimming, circuit mechanisms (L-interneurones, see Fig. 2A) might also contribute to burst termination[e,f]. The cell that is designated L (lateral) in Fig. 2A can be activated at the peak of the depolarization as shown in Fig. 2B. When this occurs, it will inhibit the I-interneurones, leading to a disinhibition of contralateral neurones and, consequently, a new burst might follow. Moreover, sensory mechanisms also contribute (compare with Fig. 3, p. 273).

Different factors that control burst onset and termination are summarized in Fig. C. For simplicity, action potentials are not indicated. Upon the release of inhibition, depolarization is initiated by activation of both NMDA and AMPA/kainate receptors as a result of background excitation. The depolarization can be increased by voltage-dependent NMDA receptor–channels and LVA Ca^{2+} channels (postinhibitory rebound excitation) that open up as the membrane potential approaches more depolarized levels. The depolarization is maintained by the NMDA plateau depolarization, by background excitation via AMPA/kainate receptors, and by the phasic excitation from the excitatory (E) interneurones. The depolarization phase is terminated by an activation of K_{Ca} channels, leading to a repolarization of NMDA plateau potentials, and spike-frequency adaptation as a result of a summation of the sAHPs in spiking E-interneurones. Upon repolarization, NMDA receptor–channels will close because of their dependence on voltage. In addition, ipsilaterally projecting excitatory stretch-receptor neurones (SRE) will contribute to the initiation of the depolarization, while contralaterally projecting, inhibitory stretch-receptor neurones (SRI) will contribute to burst termination (Fig. 3). The onset

Fig. (Right.) ***Cellular factors that contribute to burst termination.*** ***(A)*** *A schematic drawing of the synaptic excitation that occurs during a locomotor burst of sufficient amplitude to elicit an action potential. It is shown that the amplitude of the slow afterhyperpolarization (sAHP) will determine whether only one action potential or several will occur during this time epoch. A large and long-lasting sAHP will make the bursts shorter, everything else being equal.* ***(B)*** *Ca^{2+}-dependent K^+ channels (K_{Ca}) not only cause the sAHP but will also promote the termination of plateau potentials of the type elicited by voltage-dependent NMDA receptor–channels. It is shown that a short-lasting plateau potential (black trace) is prolonged markedly if the plateau potentials are blocked by apamine (grey line).* ***(C)*** *Several different factors contribute to the initiation of a depolarizing phase, the maintenance of a depolarization, and the termination of this phase. In addition to conventional synaptic excitation, voltage-dependent NMDA receptors and low-voltage activated Ca^{2+} channels (LVA-Ca) are activated. Through these channels, Ca^{2+} will enter the cells, and cause a progressive increase of the intracellular concentration of Ca^{2+} causing an activation of K_{Ca}, and thereby a progressive hyperpolarization, leading to a closure of voltage-dependent NMDA receptor–channels. The initiation of the depolarizing phase is facilitated by activation of ipsilateral excitatory stretch-receptor neurones (SRE), while the termination of the activity is partially a result of activation of contralateral inhibitory stretch-receptor neurones (SRI). Abbreviation: E, excitatory interneurone.*

therefore, it also contributes indirectly to a reduction of the K_{Ca} (Ref. 37). Thus, the co-stored DA and 5-HT exert a synergistic and complementary action. Also, in this case, the modelling was invaluable for the interpretation of the data (see Box 2).

In addition to their fast action, via ligand-operated ion channels, both GABA (Refs 38 and 39) and glutamate exert an action via G-protein-mediated and metabotropic receptors like $GABA_B$ and mGluR (Ref. 40), respectively. Activation of $GABA_B$ receptors decreases the high-threshold Ca^{2+} currents that are activated during the action potential and the low-voltage activated Ca^{2+} currents that are responsible for the postinhibitory rebound (see above). A decrease of the high-voltage activated Ca^{2+} current will result indirectly in a reduction of the AHP, thus delaying the termination of the burst on the active side, while a decrease of low-voltage activated Ca^{2+}



of reciprocal inhibition from the contralateral side will also contribute to burst termination.

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current will reduce the likelihood for a given neurone to become activated on the postinhibitory rebound, delaying the initiation of a new burst (Fig. 4B). On the network level, these cellular effects of activation of $GABA_B$ receptors will cause a slowing of the burst rate, and an increased intersegmental-phase lag. The activation of mGluR causes a depolarization of network neurones, leading to a stabilization of the motor pattern, and an increase in the burst rate[40]. Peptides, such as neurotensin, somatostatin[41] and tachykinins are also present in the lamprey spinal cord, and have an action on the cellular and the network level. However, their role is not yet well defined.

Presynaptic modulation occurs in both locomotor interneurones and afferents

In lamprey, as in invertebrates and other vertebrates, a presynaptic modulation of the afferent synaptic transmission occurs during locomotion (Fig. 5A) that decreases the synaptic efficiency in certain phases of the movement cycle[43,44]. The role of this modulation appears to be to provide a gain control, and to gate the sensory input, so that it will not have the potential to disturb the locomotor pattern, except in the 'appropriate' phases of the movement cycle.

Surprisingly, the axonal terminals of both I- and E-interneurones were modulated during each locomotor cycle[46,47], by a combined action of both $GABA_A$ and $GABA_B$ receptors (Fig. 5B). This means that the efficiency of both the inhibitory and excitatory transmission is modulated phasically, and can be gated at different levels. The phase relationships are such that the crossed axons of I-interneurones should have a reduced efficiency in the period during which a burst occurs on the side of the axon but have its full effect when the other side of the segment is active. This might be a mechanism to ensure that, in particular, long inhibitory axons do not interfere with the local burst generation in the segment. It would thus seem that there is, along the spinal cord, a local control of the synaptic transmission from E and I network interneurones by GABAergic cells that are most likely of a multipolar type (but see Ref. 4). They do not affect the reticulospinal cells, which instead are subject to a 5-HT-induced presynaptic inhibition locally along the cord. This latter mechanism would thus enable local circuits at the segmental level to control the effects of the supraspinal input.

Co-ordination of the locomotor circuitry along the spinal cord

During regular forward swimming, the different segments along the spinal cord are co-ordinated with a constant phase delay of 1% from the rostral to caudal end (see Fig. 1A and Refs 48 and 49). A similar phase lag also occurs in the isolated spinal cord that is activated by glutamate-receptor agonists. Therefore, the spinal cord is essentially arranged so that it tends to produce the motor pattern that underlies forward locomotion under resting conditions[11,50,51]. This lag is, however, variable and can vary 'spontaneously' from approximately +2% (forward swimming) to a value of –1%, which corresponds to backward swimming[50]. The spinal motor co-ordination is thus flexible. The phase lag can be varied experimentally in a reproducible fashion, such that an increased excitability in the rostral spinal cord will increase the phase lag along the entire spinal cord[50,51], whereas a local increase over the caudal end of the spinal cord will reverse the co-ordination along the entire spinal cord, and produce a pattern that is similar to that of backward swimming[50]. Essentially, the area of the spinal cord with the highest excitability will become the leading segment, and from this area all segments

Box 2. Computational analysis of central pattern generator of lamprey

The primary aim here is to account for how the neural network operates in terms of nerve cells rather than as abstract oscillators, therefore the nerve cells of the network in Fig. 2A (p. 272) were simulated in a realistic manner[a,b], with different voltage-dependent (Na^+, K^+, Ca^{2+}), Ca^{2+}-dependent K^+ channels, and ligand-gated ion channels (AMPA/kainate, NMDA and glycine). Nerve cells were simulated with the defined properties of each particular cell type. When a population of, for example, excitatory (E) and inhibitory (I) cells were simulated, the input resistance was made to vary with, for example, ±10–15% to simulate the biological variation[c], and to avoid synchronization of the cells in one population, as would occur if all cells were identical. Next, the model cells were connected in a way that corresponded to that occurring in the biological network (Fig. 2A). The model network that is represented here could generate rhythmic burst activity, with a pattern of neuronal activity that corresponds to that observed experimentally. Locomotor activity could be initiated and driven from simulated reticulospinal neurones. The reticulospinal EPSPs are mixed, and the relative proportion of NMDA to AMPA/kainate receptors can vary markedly. To achieve a large range of burst frequencies, the simulated reticulospinal neurones had to produce a relatively high contribution from NMDA receptors, compared with AMPA/kainate receptors at low rates of 'swimming'. To achieve a higher burst rate, the relative contribution from AMPA/kainate had to be increased[d,e]. Figure A shows simulated activity in the segmental network, elicited by activation from two model reticulospinal neurones (R) and, in this case, mediated via AMPA/kainate receptors only. The rhythmic activity of the lateral (L), excitatory (E) and crossed inhibitory (I) interneurones on either side occurs in strict alternation with the corresponding cells on the contralateral side. The model of the spinal network could also be activated by a simulated application of NMDA or AMPA/kainate in the bath. Different levels of drive could make the simulated network cover the entire normal physiological range of bursts, with the appropriate pattern of activity. The network model responds to a simulated activation of the 5-HT system in the same way as its biological counterpart[b], that is, a reduction of the slow afterhyperpolarization (sAHP) in the simulated network interneurones will result in longer bursts and a lowering of the burst rate.

The sensory control[f,g] was also modelled. Stretch-receptor neurones (SRE and SRI, Fig. 2A) were connected to the spinal network[h,i], and the bending movements, which occur during swimming, were simulated by applying a sinusoidal current to the stretch receptors on the left and right side, and with a 180° phase shift[d,i]. Indeed, if the superimposed sinusoids were somewhat faster or slower than the basic network activity, the central network activity did adapt to the external frequency, at both above and below the resting burst rate. In principle, this is similar to what has been observed experimentally (Fig. 3A, p. 273). It shows that the sensory input in the circuit configuration revealed experimentally can produce both an earlier and a delayed burst termination effectively as in the lamprey network. From the simulation, we have thus learned that the network components, defined so far, can account for the present findings, at least to a first approximation, and it is therefore likely that we might have captured essential facts about the basic mode of operation of this locomotor network.

To study the neural mechanisms that underlie the intersegmental co-ordination, 60 segments of the type described above were simulated, with long descending axons (20 segments) from I-interneurones, and shorter E-interneurone axons that extend in both the ascending and the descending direction (six segments). The model was made continuous with no explicit segmentation to mimic the natural situation[k]. A general and equal excitatory drive to the entire chain results in a rostral-to-caudal intersegmental phase lag, as during forward swimming (Fig. B). This lag increases along the entire spinal cord if the excitability in the most rostral segments is increased selectively. If, instead, the caudal part is excited locally, the phase lag will become reversed, as in backwards swimming. The established circuitry with its difference in longitudinal distribution will thus produce a lag along the spinal cord that is modifiable, as under natural conditions. The phase lag along the spinal cord remains constant (around 1%) during 'real' swimming at varying rates but in the model with constant excitability along the entire cord it might vary somewhat (from 0.5–2%) and, presumably, some further addition of membrane

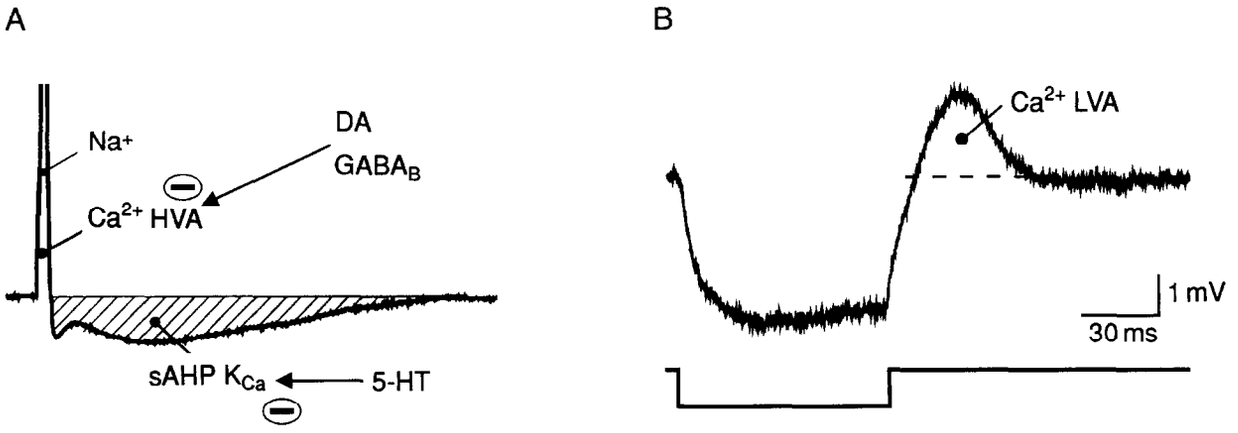

Fig. 4. ***Fine tuning of cellular properties produced by GABA, 5-HT and dopamine.*** **(A)** *The effects on Ca^{2+}-dependent K^+ channels (K_{Ca}) which produce the afterhyperpolarization (sAHP). Dopamine and GABA act on the high-voltage-activated (HVA) Ca^{2+} channels, which in turn are responsible for the Ca^{2+} entry during the action potential. Dopamine and GABA causes a reduction of the sAHP by reducing the entry of Ca^{2+}, whereas 5-HT reduces the sAHP by a direct action on K_{Ca}.* **(B)** *The postinhibitory rebound produced by a cell after a hyperpolarizing pulse. This postinhibitory depolarization is due to activation of low-voltage-activated (LVA) Ca^{2+} channels, occurring in I-interneurones and in other cell types. These channels are depressed by $GABA_B$-receptor agonists.*

properties is required to obtain a constant coupling over the entire frequency range.

A simulation of the actual swimming movements of the lamprey, using a combined neuronal–mechanical model[17] is shown in Fig. C. The model incorporates the electromechanical transformation of the neuronal output of the network into muscle force, the viscoelastic properties of the body, the interactions with the surrounding water, and the sensory-feedback control that is exerted by the stretch-receptor neurones. Frames show steady-state swimming at 4 Hz, resulting from tonic excitation of the network, with the model lamprey moving forwards at a speed of 0.73 m s^{-1}. The interval between frames is 50 ms. Grid size is 2 × 2 cm.

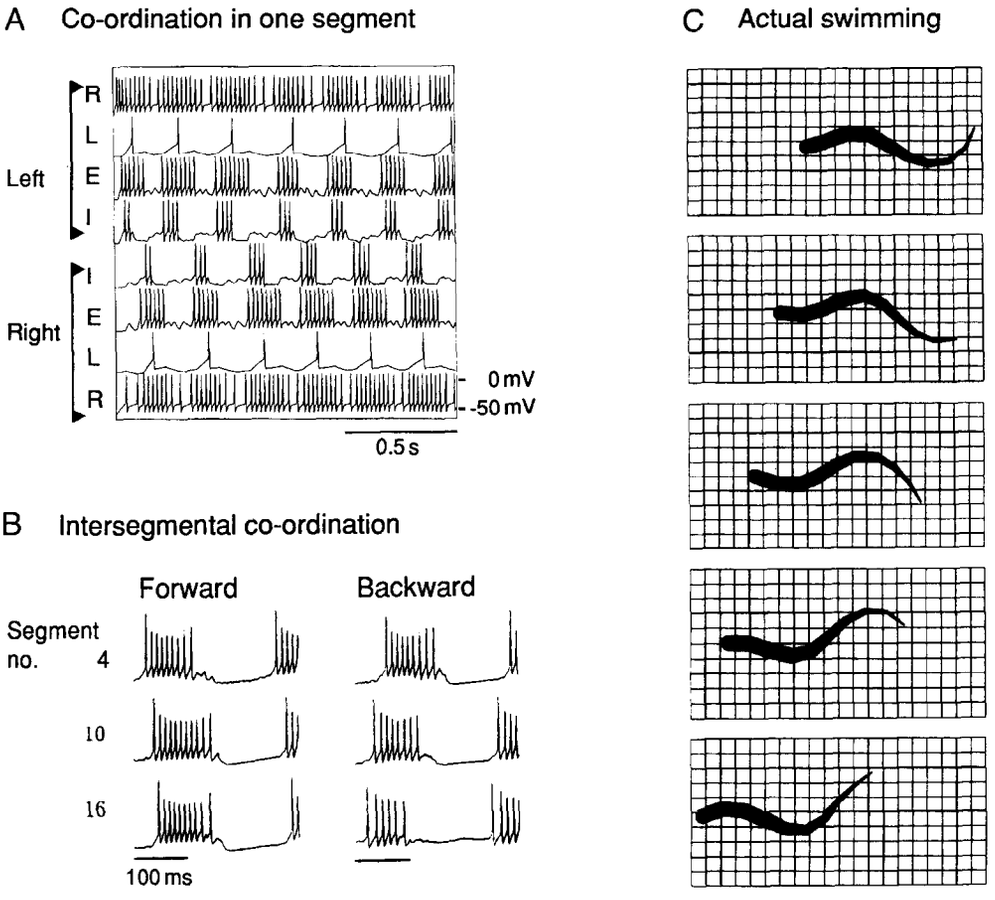

Fig. ***Simulation of the segmental and intersegmental co-ordination in lamprey.*** **(A)** *A realistic simulation using a pool of excitatory (E), inhibitory and crossed (I) interneurones and lateral (L)-interneurones. The activity is driven by excitatory reticulospinal (R) neurones. Activity on the left and right side alternates.* **(B)** *The pattern that is produced by a simulated network of 60 segments in which the distribution of axons along the cord is included (see text). It is shown that this network will produce a phase lag along the simulated spinal cord, and that this phase lag can be reversed if the excitability is increased in the caudal end of the body (see also Fig. 1).* **(C)** *The viscoelastic properties of ten successive myotomes have been simulated together with the viscous properties of the water. The mechanical model is controlled by a simplified neuronal network with properties similar to that of the neuronal network shown in* B *(see text).*

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in the rostral or caudal direction, or both, will follow with a similar phase lag, segment after segment. This means that the value of the phase delay can be controlled by a very simple neural mechanism. By adding a little extra excitation to the rostral or caudal area of the spinal cord, the phase lag can be varied from +2% to −1%. Behaviourally, the phase delay varies not only between forward and backward swimming but also during other conditions in which more than one undulatory wave is present on the body (narrow swimming). Thus, there is a need for higher centres to control the phase lag, and a very simple neural mechanism seems to be sufficient. Most, but not all, physiological features of intersegmental co-ordination (Box 2) can, at present, be accounted for by a network model that is based on known segmental and intersegmental (Fig. 2) connectivity[52]. With abstract limit-cycle oscillators, the intersegmental co-ordination has been simulated with an asymmetric coupling[53] with a constant phase lag, and with simple non-spiking model interneurones in a somewhat different configuration[54,55]. These models can also produce a lag between the two or more segments simulated. There is as yet no consensus between the different research groups that are addressing the neural bases of intersegmental co-ordination (for review, see Refs 49 and 56).

So far, we have considered only the neural motor pattern, and how it is modulated by sensory signals. In reality, however, the CNS controls the muscle fibres along the body that produce the undulatory propulsive wave. The successive muscle compartments have also been modelled with their viscoelastic properties, and the viscous properties of the water[57]. A 'mechanical model lamprey' that was controlled by a neuronal network similar to that described above was designed. This mechanical model can swim forward and backward over the computer screen with normal undulatory movements (Box 2). Moreover, it can be made to turn, by adding briefly an extra tonic excitatory drive to one side. Moreover, the process of turning looks very similar to that occurring in 'real' life. This addition is of obvious importance for addressing the neural mechanisms of goal-directed locomotor behaviour.

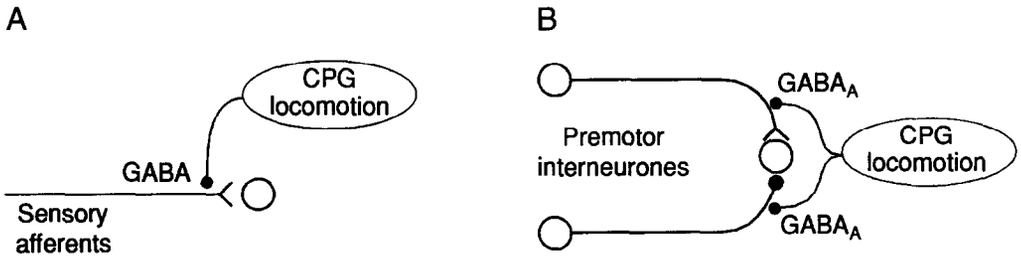

Fig. 5. ***Schematic representation of locomotor-related presynaptic inhibitory effects.*** **(A)** *Sensory afferents receive a phasic presynaptic modulation from the locomotor central pattern generator (CPG), a type of modulation that occurs in mammals, such as the cat*[42]*, and in lamprey*[43] *and crayfish*[44]*. In most instances, it has been shown that GABA mediates the presynaptic modulation that occurs in each locomotor cycle.* **(B)** *Presynaptic modulation occurs in the axon terminals of both excitatory and inhibitory premotor neurones in the locomotor network in lamprey. These effects are a result of a phasic modulation, involving both $GABA_A$ and $GABA_B$ receptors, from the CPG, most likely via multipolar GABA cells. This type of effect has also been observed in the presynaptic terminals of phasically modulated nerve cells in the stomatogastric ganglion*[45]*.*

Control of body orientation

Lamprey, like many other aquatic animals, maintain their body orientation in the vertical plane (posture) primarily with the help of vestibular reflexes, while the visual system plays a secondary role[58]. The lamprey orientates well in the dark with the help of the vestibular apparatus but, if light is present, this can also affect the body orientation. Normally, the lamprey swims with its dorsal side up, and any deflection from this position (roll tilt) produces a corrective motor response. To study this control system, stabilizing the dorsal-side-up position, a brainstem preparation with intact vestibular apparatus and eyes was developed *in vitro* in which vestibular afferents and reticulospinal neurones could be recorded while the brainstem was subjected to roll tilt of various angles, from 0° (normal position) to 180° (Refs 59 and 60) (Fig. 6A).

Input to the postural-control system of the brainstem is formed mostly by otolith afferents of the vestibular organs, which are excited with ipsilateral roll tilt[61]. They activate contralateral reticulospinal neurones polysynaptically (Fig. 6B). The different reticular nuclei respond maximally at different degrees of tilt: neurones in the mesencephalic reticular nucleus respond maximally at 45°; neurones in the anterior rhombencephalic nucleus respond maximally at 135°; and neurones in the middle and posterior rhombencephalic nuclei respond maximally at 90° (Ref. 62). These findings enabled the formulation of a conceptual model of the roll-control system (Fig. 6D). Deflection from the normal, dorsal-side-up position elicits an activation of the vestibular afferents on the side rolling down, which excites contralateral reticulospinal neurones. The latter send a command to the spinal cord, which elicits a corrective motor response to restore the normal body orientation (Fig. 6D). The left and right subpopulation of reticulospinal neurones elicits a roll in the opposite direction. The system for the body orientation control has an equilibrium point at 0° (the dorsal-side-up position; Fig. 6D). At this position, the effects of the two subpopulations of reticulospinal neurones are equal to each other, and no corrective motor response will occur. A unilateral illumination (Fig. 6C) might, in addition, elicit a bias in the response to roll [Fig. 6D (E)]. Consequently, the equilibrium point will be shifted towards the illuminated side, and this new position will be stabilized by the gravity orientation system, that is the dorsal side of the body will be turned towards the light.

By using this lamprey model, essential features of the postural-control system have been revealed, that is, (1) a stabilization of posture by means of two opposing vestibulo–reticulospinal pathways, (2) capacity of the gravity orientation system to stabilize different positions, (3) initiation of a movement by a shift of the equilibrium point of the postural-control system, (4) an explanation for the continuous rolling movement following the removal of one labyrinth[58], and (5) interaction of sensory inputs of different modalities[63,64].

Concluding remarks

The neural mechanisms that underlie locomotion and body orientation in lamprey are now understood in many respects. The control system of the lamprey, phylogenetically old among vertebrates, has most likely evolved and been modified to encompass the control of fins and limbs. Although the locomotor behaviour in lamprey is much simpler than that occurring in terrestrial vertebrates, it appears likely that the basic mode of operation of this control system is similar in all vertebrates[1].

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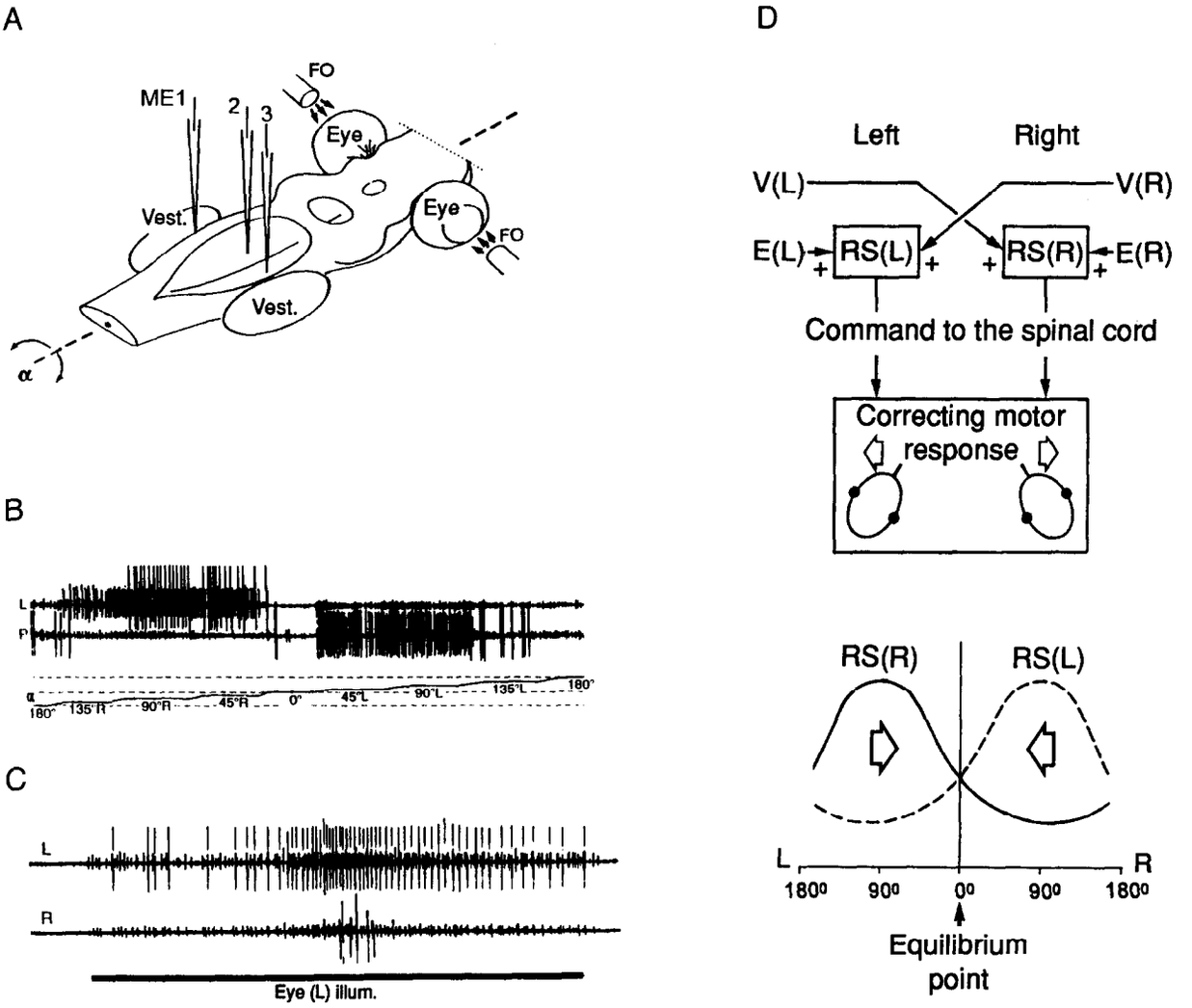

Fig. 6. *Control of body orientation.* *The lamprey normally swims with dorsal side up, and any deflection from this position, that is, roll tilt, is counteracted by the postural-control system.* **(A)** *The experimental arrangement for studies of the roll-control system* in vitro. *The brainstem with intact vestibular organs (Vest.) and eyes could be rotated around its longitudinal axis (±180°; angle α). Eyes could be illuminated by a fibre-optic light source (FO). The activity of vestibular afferents, as well as of reticulospinal neurones from different nuclei, was recorded by microelectrodes (ME1–3).* **(B)** *The response to tilt in reticulospinal neurones recorded extracellularly from two symmetrical points [left (L) and right (R)] in the middle rhombencephalic reticular nucleus. The neurones are activated with contralateral roll tilt.* **(C)** *The response to eye illumination (recordings from approximately the same points as in* B*). Activation on the ipsilateral side prevails. In some experiments, inhibition on the contralateral side was observed.* **(D)** *The conceptual model of the roll-control system.* **(Top.)** *Vestibular input (V) excites the contralateral RS neurones preferentially, while the input from the eyes (E), excites the ipsilateral neurones. The two subdivisions (***left** *and* **right***) of the reticulospinal system produce reciprocal effects in the spinal cord, resulting in rotation of the animal in opposite directions.* **(Bottom.)** *The characteristics of the roll-control system. The two subdivisions of the reticulospinal system, driven by vestibular inputs, are activated with opposite roll tilts. They elicit the rotatory effects in opposite directions (arrows). The intersection of the two curves corresponds to the equilibrium point of the roll-control system.*

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