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Metachronal propagation of motor activity

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1. ABSTRACT

A diverse array of biomechanical systems has evolved to satisfy locomotor requirements (reptation, swimming, walking, etc.) and in all cases, successful behabior achievement requires the integrated functioning of various segments, to ensure the appropriate positioning of the different body regions. From comparative studies on a variety of invertebrate and vertebrate organisms, it is now established that the basic motor patterns underlying limb and/or trunk movements during locomotion are driven by central networks of neurons, so-called central pattern generators (CPGs). In limbless animals such as leech, lamprey, snakes... body propulsion is driven by alternate left- right trunk muscle contractions that occur sequentially (or metachronally) along the body length. Here, we highlight some common principles of motor control involving metachronal activity that are shared by multisegmental systems. In a first step we will review systems in which the neural mechanismsthe that underlie modular linear distribution have been extensively studied. Finally, we will review modeling studies that have been performed to better understand the fundamental mechanisms that underlie metachronal propagation

2. INTRODUCTION

Body displacement is at each step a challenge to motor control since it requires two conflicting functional issues to be reconciled: (1) the rupture of the static postural position in order to progress from one place to another and; (2) the step-by-step preservation of overall balance in order

to achieve an adequate behavioral requirement. The maintenance of this dynamic equilibrium during body propulsion, involves complex synergistic postural regulation requiring the integrated functioning of all the body musculature, including hind- and forelimb, trunk and neck muscles. Surprisingly, most studies devoted to understanding locomotor control in humans and animals (1-3), have mainly addressed the functioning of the neural circuits controlling leg movements (see elsewhere in this volume), and relatively little is known of the functioning of neuronal networks that activate trunk muscles in coordination with limb movements (4-7). Nevertheless these latter studies have repeatedly shown that the back muscles are rhythmically activated during locomotion, suggesting that the preservation of the dynamic equilibrium needed to displace the body can only be achieved through the appropriate coordination of trunk and hindlimb motor circuitry. Moreover, understanding how locomotory behavior is achieved in limbed animals requires investigating the mechanisms that give rise to neuromuscular activation at these various levels as well as the coordinating mechanisms of trunk and hindlimb premotoneuronal networks.

Our work over the last years has been devoted to this issue, through the investigation of both humans and animals. In this context, understanding the functioning of axial dynamics that regulate trunk activity is of importance, since as a pillar of the body architecture, it is an essential component of locomotion. However its role and the study of mechanisms involved in its functioning have often been neglected in mammals. In other species, in particular, those that use an anguilliform locomotion (leech, lamprey and *Xenopus* tadpole), the mechanisms of trunk movement generation have been investigated. One essential characteristic common to all these systems is the presence of a metachronal wave, which propagates segment-by-segment in the central nervous system. The term metachronal was created to address the way by which an activity is temporally organized according to a sequential propagation between adjacent elements, and metachronality (or propagation of signals) is only found in systems that exhibit an organization made of duplicated elements. This type of activity is founded in multi-articulated or multi-segmental systems such as those described below. Surprisingly, this pattern of activation is one of the most ubiquitous since it is found from motile hair cells and ciliated unicellular organisms to the spinal networks of vertebrates, including mammals.

The objective of this review is to highlight some common principles of motor control involving metachronal activity that are shared by various multi-articulated or multisegmental systems. In a first step we will review various systems in which this type of modular linear distribution has been extensively studied and for which data are available about neural mechanisms deciphered through the use of in vitro preparations in particular of invertebrates (8, 9), and in a second step we will review more recent data that we have collected in rats and humans.

3. METACHRONAL PROPAGATION IS AN UBIQUITOUS PATTERN

3.1. Hair cells and ciliate protozoans

The term metachronal propagation was first used to assign the activation pattern of active motile cilia that is expressed by a large number of cells or unicellular organisms. In an aqueous environment, these structures lead either to a movement of the cell itself or to an excitement of the outside milieu to facilitate the search for food. Passive sensory cilia may also be on the surface of some specific cell in metazoans. Their roles and structure may be also very variable: they can control the movement and the distribution of mucus (as it is the case in bronchial tissue) or they can be used to transform a mechanical wave into neural input (ciliate cells of the cochlea). In these cases, metachronality is generated by the coordinated activity of numerous cilia, with each cilia being slightly phase shifted with respect to its neighbor. The result is a series of waves of activity that moves across the surface of cilia. However, the mechanism by which a set of cilia beats in a metachronal fashion is still not completely solved. Machemer (10) claimed that the membrane voltage and the level of intracellular calcium had an influence on the direction of the metachronal wave. Alternately, it has been suggested that this phenomenon was essentially based on hydrodynamic coupling (11).

3.2. The leech

Numerous studies have been conducted on various motor behaviors in the leech including swimming and crawling, all of these behaviors exhibiting a metachronal propagation of motor activity. Swimming has been the most studied behavior, and less information is available for crawling. Together, these studies have led to a precise knowledge of the leech's central nervous system structure that consists of 32 ganglia interconnected by two interganglionic nerve tracts (Figure 1A). The neuronal architecture of segmental ganglia has been well characterized and is preserved from one ganglion to another.

3.2.1. Swimming

The quasi-sinusoidal undulations that characterize leech swimming result from the alternate contraction and slackening of two types of segmental muscles. First of all, the leech body is flattened to form a ribbon stretched out by tonic contractions of the ventral muscles. Then, the contraction and slackening of the dorso-longitudinal muscles (respectively VLM and DLM) act against the substratum, with a cycle period of about 0.3-1s, to generate a rhythmic curvature in the body segments (12). The metachronal phase-shift of about 20 degrees per segment, generates the wave of rostrocaudal activity (13). When the ganglionic chain is isolated *in vitro*, the recorded fictive locomotion exhibits a longer cycle period (0.5-2s) and a reduced metachronal phase shift of about 10 degrees per segment (14) which, however, increases to 40 degrees when the preparation is reduced to only two segments (15). Therefore sensory feedback appears to play a significant role in establishing swimming period. It was also shown that serotonin is a critical neurotransmitter for the

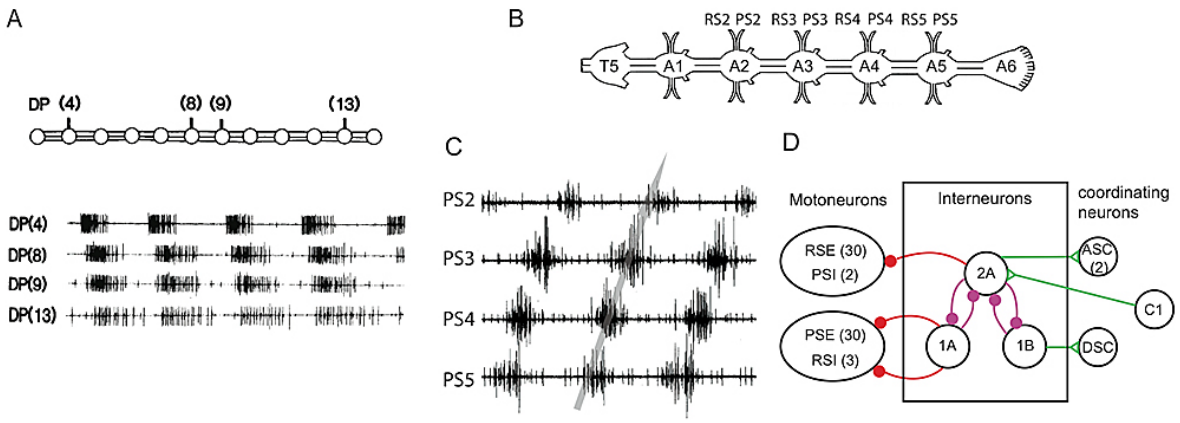

Figure 1. Intersegmental propagation of the motor activity in the leech and the crayfish. (A) Recordings from 4 DP nerves (4,8,9,13) of the activity of motoneurons of the leech during swimming (Adapted from 15). (B) Schematic of the crayfish nervous system (Adapted from 133). Ganglia responsible for the swimmeret activity are A2, A3, A4 and A5. (C) Extracellular recordings from the power stroke of the 4 ganglia showing a caudo-rostral activation of the motoneurons. (D) Diagram of the local circuit of one ganglion responsible for one swimmeret activity. The open circles represent neurons, filled circle represent inhibitory synapses and open triangles represent excitatory synapses. The numberes in parentheses are the number of the type of neurons it is associated with (Adapted from 30). C1 neurons receive inputs from all the other ganglia, ASCs and DSC send their axon to repectively previous and next ganglia.

expression of swimming rhythmic activity (16). During 5-HT bath-application or stimulation of swimming command neurons, each ganglion is able to generate weak episodes of rhythmic activity. Although neural networks in each ganglion include a unitary oscillator, the capability for each ganglion to generate a swimming-like activity is not uniform. Therefore, the system is based on strong interconnections between segments in order to create strong oscillations from weakly oscillating subunits (17).

Thirteen oscillating interneurons involved in swimming have been identified in most of the ganglia (from M2 to M16) according to the following criteria: (1) their membrane potential is in-phase with the swimming rhythm; (2) intrasomatic current injection shifts the swimming phase; (3) they make synaptic interactions with other oscillating inhibitory interneurons. Some of the interneurons that satisfy all these criteria are located in the dorsal and lateral parts of each ganglion. Their axons span up to 7 segments. While in a given segment the phase of motoneurons discharge is 180 degrees, the interneuron discharge phase exhibits a range of variations (40-50 degrees or 130-170 degrees or 220-260 degrees; (17)).

3.2.2. Crawling

Crawling in the leech is a rhythmic activity with two main activity phases, elongation and contraction, which are coordinated with the anchorage and the release of the anterior and posterior suction cups. This pattern has been recorded in the semi-intact animal and in the isolated nervous system (18). *In vivo*, a single crawling step is performed within 3 to 10s while *in vitro* it can increase up to 20s (19, 20). In a given segment, crawling results from alternating bursts of action potentials in motoneurons innervating the circular and longitudinal muscles. *In vitro*, it can be elicited by bath-application of dopamine, and a single segment can exhibit a crawling-like activity (21). Furthermore a recent study showed that crawling depends both on long-distance descending and local couplings (22).

3.3. The crayfish

Swimming in this animal requires the use of 4 pairs of swimmerets that beat periodically to move it forward. Each cycle begins with a phase of propulsion (power-stroke), produced by the most caudal pair of swimmerets that move in a bilaterally synchronous manner. The swimmerets are active in a rostrocaudal metachronal progression, with the same cycle period and a constant phase relationship that is independent of the cycle period itself. The phase lag between segments is approximately 25% of each cycle (Figure 1C). Cholinergic agonists can modulate the beating period (23), and when the system is uniformly excited, neither phase lags nor motor burst durations are modified as the cycle period. Mulloney (24) showed that there was no significant difference in the excitability of the various segments.

The isolated abdominal nervous system can produce a motor activity similar to that observed *in vivo* (Figure 1A, 25). These periodic movements are coordinated by means of approximately six hundred neurons located in each of the four pairs of ganglia. Each swimmeret pair is innervated by the corresponding segmental ganglion (for review see: 26), which generates motor bursts for power-stroke and return-stroke (27). Each segmental module contains four types of neuron (Figure 1C, 28). Each module also includes three types of non-spiking interneurons that contribute to motor pattern generation, and which send their axons to the other ganglia (28, 29). Among these three interneuron types, two are active during the power-stroke and send their axons in the ascending direction, while the third type, which is active during the return-stroke, sends

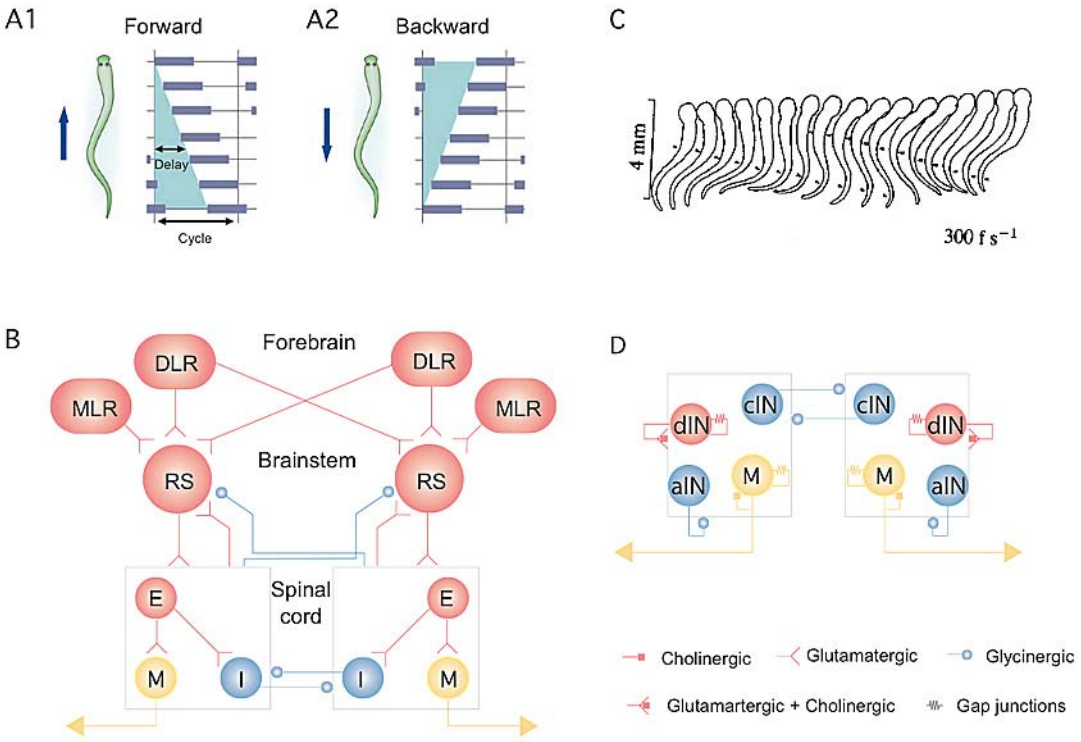

Figure 2. Organization of tadpole and lamprey CPGs. (A) Drawing of the movements of the tadpole during a swimming cycle (Adapted from 134). Arrows are pointing at the body curvatures, emphasizing a rostro-caudal bending activity during swimming. (B) Schematic representation of the tadpole swimming CPG. It is composed of 2 identical half segment (grey squares) connected by inhibitory connections coming from cINs (blue filled circle). Each half-centre has 3 populations of interneurons (cINs, aINs, dINs) connected to each other and MNs. Blue filled circle connections are inhibitory and red are excitatory. Resistor symbols indicate electrical coupling between MNs and between dINs. (C) The lamprey swims (forward or backward) by producing a metachronal wave of activity. (C1) Forward swimming produces a rostro-caudal propagation of activity with a constant phase lag. (C2) This propagation can be reversed into a rostrocaudal wave during backward swimming. (D) Schematic representation of the neural circuitry that generates rhythmic locomotor activity in the lamprey. All neuron symbols denote populations rather than single cells. For the spinal cord a unique segment is represented. It is composed of two identical half segment (grey square), within 3 populations of neurons can be found: The excitatory interneurons (E) exciting all types of spinal neurons ; the inhibitory glycinergic interneurons (I) that cross the midline to inhibit all neuron types on the contralateral side, and motoneurons (M). The reticulospinal (RS) glutamatergic neurons excite all classes of spinal interneurons and motor neurons. They receive excitatory synaptic input from the diencephalic and mesopontine locomotor regions (DLR and MLR respectively, Adapted from 98)).

its axon caudally (Figure 1D). These interneurons have little influence in the ganglion where their somata reside, but they have a strong action in triggering the activity on target ganglia through their synapses with non-spiking interneurons. Recently, it has been shown (30) that a neuron (C1) present in each ganglion, receives information from the other ganglia and accordingly adjusts the timing of the local CPG for the next burst.

3.4. The lamprey

In this most primitive vertebrates, swimming results from undulations which propagate along the body and produced appropriately-timed forces against the water, thereby producing forward body displacement (31). The undulating movements of the lamprey are produced by right and left alternating bursts of activity and a rostrocaudal activation of the axial muscles (Figure 2A1). This sequential activation is due to a lag of bursting activity in neighboring segments (1 % of a cycle duration). However, this rostrocaudal directed activation can be inverted to allow backward movement (Figure 2A2).

Locomotion can be induced by stimulating the diencephalic (32), or mesencephalic regions (33) of the brain. These two regions send projections to reticulospinal neurons (RS) which in turn activate the spinal central pattern generators (CPGs) that generate the locomotor activity (34). The speed of locomotion is determined by the firing level of these supra-spinal locomotor regions (35). Subpopulations of RS neurons have been shown recently to be activated depending on the direction of locomotion (36).

Fictive locomotion can be induced in the isolated spinal cord by bath-application of excitatory amino acids (37). This *in vitro* elicited motor pattern exhibits a range of frequencies (0.25-10Hz) and phase values similar to those

observed *in vivo* (Figure 2A, C1, 38). Backward fictive swimming can be also induced, by applying a stronger excitation to caudal spinal segments. In this condition, these segments become active at a higher frequency than in the rostral cord, and then rhythm onset and bursting activity propagate in a metachronal caudorostral manner (Figure 2C2 39).

The spinal cord which encompasses about 100 segments, can be divided transversally into pieces that still produce a rhythmic activity, although when less than 4 segments are retained, the rhythm regularity is strongly altered (37). It has also been reported that following a longitudinal hemi-section, which separates the right and the left sides, the rhythm frequency increases due to the severing of crossed glycinergic fibers (40). Therefore, the reciprocal inhibition between opposite hemi-segments in the intact cord ensures left-right alternation and decreases the locomotor frequency (41).

The mechanisms of burst generation in a hemi-segment depend on ipsilateral excitatory interneurons (42). The kernel of the locomotor network in the lamprey consists of ipsilateral glutamatergic interneurons and glycinergic interneurons with contralaterally-projecting axons. The excitatory interneurons thus give rise to inhibition on contralateral motoneurons through these crossed inhibitory interneurons (Figure 2B). The latter consist of two types: (1) large interneurons with a long caudally-projecting axon; (2) small interneurons with shorter axons (43), which produce inhibitory postsynaptic potentials of larger amplitude. Small size ipsilateral glycinergic interneurons are co-activated with motoneurons and provide a monosynaptic inhibition of motoneurons and crossed inhibitory interneurons (44). These glycinergic interneurons are not required for burst generation. Motoneuron activity is dependent on both their membrane properties and synaptic inputs. During the first part of the swimming cycle, they are excited via NMDA and AMPA/kainate receptor activation, and during the second part of the cycle, they receive a glycinergic inhibition.

3.5. The larval zebrafish

Previously considered as a model system for studying development, the larval zebrafish (2-6 days) has proven useful in deciphering the neural circuitry involved in locomotor behaviors due in particular to genetic and optical accessibility of this animal (45-48). In this review we will focus on two of its behaviors: swimming and struggling behavior.

3.5.1. Swimming

The zebrafish larva can produce both slow and fast swimming patterns (48-50) that have been shown to involve body bends that travel rostrocaudally (50, 51). Motoneuron and interneuron recruitment depends on swimming frequency (52). These authors also showed that there was a correlation between neuronal location and swim frequency. Neurons that are ventrally located in the spinal cord are activated at low frequency whereas an increase in frequency leads to gradual recruitment of excitatory neurons located more dorsally. As the swimming frequency increases, motoneurons fire at a higher rate and more and more cells are recruited, thereby leading to an increase in the pool of active motoneurons when the frequency increases. In contrast, the recruitment of interneurons showed silencing of premotor interneurons driving movements at lower speeds associated with recruitment of more dorsally-located interneurons (53). The recruitment of inhibitory interneurons follows an opposite pattern (52). Altering ventrally located excitatory interneurons perturbs the slow swimming pattern only, thereby leading to the hypothesis that different spinal circuits are involved in adjusting the swimming speed (52).

3.5.2. Struggling behavior

When confronted by a mechanical stimulus (a tap), a larval zebrafish, like other fish, turns away from it to escape the potential threat. The response varies depending on the location of the stimulus. Tapping the tail evokes a weak and slow response whereas the same stimulus applied to the head triggers the largest and fastest turns (54, 55). This behavior has been shown to involve body bends that travel caudorostrally (56). CiD neurons are ipsilateral descending excitatory interneurons. Dorsal CiDs excite motoneurons and receive a direct input from the Mauthner axon (55, 57), which initiates the escape. Bhatt *et al.* (55) have shown that most of these neurons are activated during a weak response. For strong struggling behavior, however, all neurons fire with a largest level of activity (55). It does not seem that struggling behavior involves the recruitment of different pools of CiDs according to the intensity of the response (55).

3.6. The tadpole

The tadpole of *Xenopus*, an anuran aquatic amphibian, has a mode of locomotion similar to that of the lamprey and leech in that propulsion of the animal is ensured by applying forces against the water, again through the propagation of a metachronal wave along the body (Figure 2C). It is one of the simplest models for studying spinally generated motor behavior. During development, the tadpole passes through various stages with profound changes in locomotion. In the present review, we will mainly focus on postembryonic stage 37/38, at which the embryo contains about thirty segments.

Two types of motor activity can be observed: swimming and struggling. These two locomotion-related behaviors essentially involve the same populations of neurons with more neurons being active during struggling. Two opposite patterns of motor activity are produced: (1) a rostrocaudal wave with a short period (40-100ms) during swimming; and (2) a caudorostral wave with a longer period (>100ms) during struggling (58). However, when the same neurons are involved in these two behaviors they do not exhibit the same firing pattern. During swimming a single action potential per cycle is produced in premotor interneurons (59) while during struggling, bursts of action potentials are produced. The initiation of one or the other behavior depends on the spinal cord stimulation: a chemical or electric stimulation of weak amplitude elicits episodes of swimming, while stimulations of larger amplitude give rise to struggling behavior (58).

Swimming starts from the head and then progresses towards the tail (Figure 2C). A metachronal propagation is observed with a delay of 1.5 to 5.5ms/mm (60). When induced by a brief sensory stimulus, the swim frequency begins at around 20-25Hz then decreases, first quickly then more slowly, to reach 10-15Hz by the end of the episode. The segmental delay does not vary significantly with cycle period in the young tadpole, but does so at later stage 42. This rostrocaudal propagation results from a gradient in neuronal excitability along the spinal cord (61). Intracellular motoneuron recordings at various sites along the cord revealed that during swimming there is a rostro-caudal decrease in both glutamatergic excitatory and glycinergic inhibitory inputs (61). This gradient may underlie a flexible mechanism for controlling the metachronal progression of motor activity. It was also shown that the capacity of the network to generate a rhythmic activity is not uniformly distributed along the spinal cord (61). Rostral regions are capable of acting as independent intrinsic oscillators (Fig2. D), generating a rhythm in response to a brief stimulus while the most caudal regions of the spinal cord can generate rhythm only if they are connected to the rostral cord regions or when they are artificially activated by bath-application of NMDA, for example (60).

Once initiated by a sensory stimulus, the locomotor rhythm remains sustained for several hundreds of cycles. In contrast to other preparations, the persistence of the rhythm does not depend on repetitive sensory stimulation or on the addition of exogenous pharmacological substances. Fictive swimming is underlain by a tonic excitation with phasic excitation during the cycle alternately with a strong hyperpolarizing inhibition in the mid-cycle. The tonic excitation is mediated through NMDA receptors (62), while the phasic excitation depends on AMPA and cholinergic receptor activation and on electrotonic coupling between motoneurons (63). The inhibition occurring in mid-cycle involves glycinergic receptors, and its strength regulates the swimming frequency. When decreased, the swimming frequency is increased. At early postembryonic stage, the presence of intrinsically oscillating neurons was not observed, and it was postulated that the rhythmicity depends mainly on CPG synaptic properties (Fig2. D) and, in particular, rebound from inhibition (64, 65).

3.7. The urodeles

Although, the metachronal propagation of axial activity has been mostly studied in legless animals (lamprey and *Xenopus* tadpole), intermediate cases exist amongst quadrupeds that are also capable of producing anguilliform type swimming such as urodeles (66, 67) but also the tadpole of *Xenopus* during the course of metamorphosis (68, 69). The studies suggested that the spinal organization governing the control of trunk movements was very close to that of true apodal animals. However, for these two models, there are few data available on the underlying cellular mechanisms. Although the spinal network organization at the early *Xenopus* tadpole stage has been precisely described (see above), the changes occurring in spinal locomotor circuitry during metamorphosis remain largely unknown (69). For urodeles, only some data are available on the overall organization of the forelimb locomotor network in nectura (70), where investigations have focused mainly on axial motor control (66, 71, 72). However, it was shown that both locomotor patterns (swimming and walking) are controlled by the mesencephalic locomotor region (73). During swimming, the animal uses a propulsion strategy similar to that of the lamprey with a metachronal propagation of axial motor activity (67). However the speed of this rostrocaudal distribution is not uniform and three different regions can be discriminated. These differences in the speed of propagation have been suggested to be related to the presence of the fore- and hindlimb neuronal networks (66). During walking the motor pattern is different with two waves of activity induced along the rostral and caudal regions of the body axis that propagate in opposite directions, and synchronous activity in the middle region of the trunk. It was suggested that this activity represents a hybrid pattern of the lamprey: the axial CPG generates a metachronal motor wave on which the limb CPGs “stack” their own rhythms when the animal switches from swimming to walking (66).

3.8. Mammals

Whereas all of the above mentioned studies have been conducted on invertebrates or lower vertebrates, recently, our attention has turned to the mechanisms involved in trunk control both in quadrupedal mammalians and humans. Our findings indicate that comparable spinal motor patterns can be observed in the rat and human.

3.8.1. Axial movements and propagated activity

Motor bursting related to trunk activation in the newborn rat, was explored both *in vitro*, using isolated spinal cord preparations, and *in vivo* at the behavioral level, to obtain the functional correlates of this activity (74-76). To assess *in vitro* how various cord regions might interact to coordinate motor activity, we performed simultaneous multi-site extracellular recordings from all thoracic, lumbar and sacral levels of the isolated spinal cord. This allowed demonstrating that the rat spinal cord has the intrinsic ability to generate an intersegmentally propagated motor activity during pharmacologically-induced locomotor-like activity (74, 75). However, motor burst propagation was found to occur caudorostrally (i.e. in the opposite direction to that occurring during lamprey forward swimming for example) and with two distinct zones of activity with different propagation velocities: the sacral cord region and in the region of segments L1 to T2. By correlating the latency of intersegmental propagation and the cycle period we found that the system adapts the intersegmental latency to the ongoing motor period in order to maintain a constant phase relationship along the spinal axis. The mean conduction time for locomotor-related bursts along the thoracic cord was 800ms, indicating that propagation between each segment may also involve local synaptic relay interactions that effectively slow propagation. However, based on the timing of motor bursts and on the presence of rhythmic elements all along the spinal cord, it was suggested that the travelling wave could not be explained solely on the basis of axonal conduction

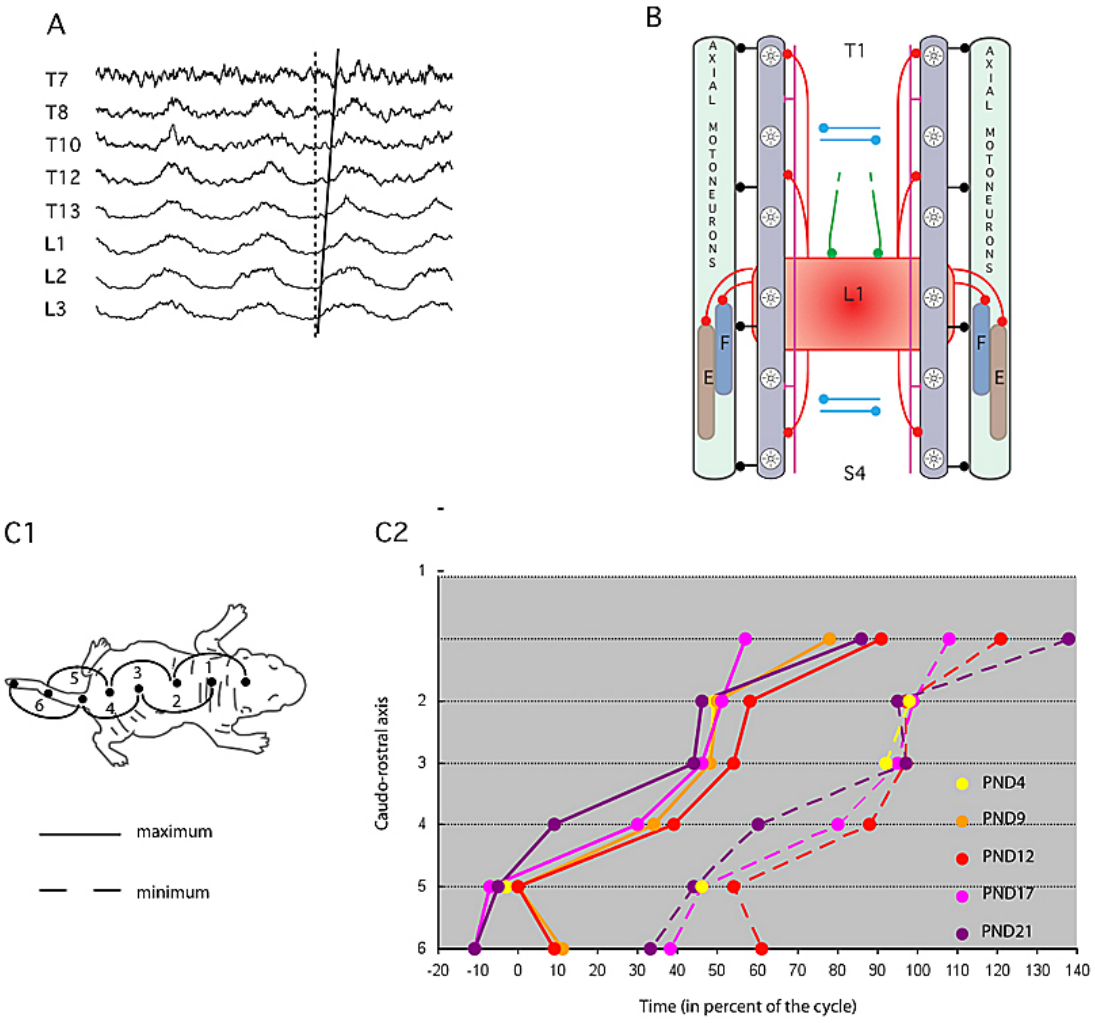

Figure 3. Motor wave propagation in the rat. (A) Caudorostral propagation of motor bursts in the isolated spinal cord. Simultaneous rectified/integrated recordings of thoracic (T) and lumbar (L) ventral roots ventral roots during locomotor-like activity induced by bath-application of 5-HT and N-methyl-D,L-aspartate. The vertical dashed line indicates the onsets of motor bursts in L2. The oblique continuous line, drawn through the onsets of motor bursts in all recorded ventral roots reveals the phase-shift between lumbar and thoracic recording sites. (B) Schematic of organization of spinal cord networks in mammals. Red box: location of hindlimb CPG. Left and right chains of highlighted circles in grey surround rhythmic elements at each segmental level. E: extensor motoneurons; F: flexor motoneurons. Horizontal blue lines represent cross-cord connections that occur along the spinal cord. Purple lines denote long propriospinal pathways also involved in longitudinal coordination. Green lines: descending commands. Rostrally and caudally-projecting influences of the lumbar CPGs are indicated in red. (C) Angle analysis of axial motor activity in the frontal plan during development. C1, Schematics indicating the position of the considered angles in the frontal plane. C2, Plots of the maximum and minimum amplitude for each angle reveal the caudorostral direction of the propagation of the maximum bending. PND: post-natal day.

velocities and synaptic transmission delays. Rather, and as suggested from previous work both in the newborn rat (74) and lamprey (77, 78), it is likely that both long multi-segmental neuronal pathways as well as local circuit interactions between adjacent segmental oscillators are involved in the coupling (79).

At the behavioral level, a 2-D kinematic analysis in freely behaving animals indicated that there is a rhythmic sequential change in trunk curvature during each step cycle (75). This rhythmic bending in the frontal plane during locomotor activity occurred in a caudorostral direction (75). Recently, we performed a much more detailed analysis using 3-D kinematics to explore trunk motion during locomotion in rats at various post-natal days (PND 4, 9, 12, 17 and 21). We examined detailed movements of the body axis (neck, trunk, and tail) in the sagittal and frontal planes during free-walking, elicited either by olfactory or visual stimulations (Figure 3C). During locomotion the spine bent rhythmically from the tail

to the head with age-related differences. In older animals, angular variations decreased in the horizontal and sagittal planes. We concluded that despite postural and developmental changes, the walking pattern observed as soon as PND 4 mostly resembled that of the adult, despite differences in movement amplitudes (76).

3.8.2. Propagated activity in lumbar and sacral segments

Interestingly, recent studies performed in decerebrated paralyzed cats during fictive scratching (80, 81), revealed that a rostrocaudal propagation of electric wave (velocity 0.3m/s), can be observed in lumbosacral spinal interneurons. This study used a multielectrode array system that was positioned dorsally on the lumbosacral spinal cord. The duration of the flexor phase, but not of the extensor phase, was highly correlated with the cycle duration of the travelling waves with a mean propagation speed of 0.3m/s (81).

In the mouse, Bonnot *et al.* (82) studied the activity of motoneurons in the isolated lumbo-thoracic and sacral spinal cords. Calcium imaging of motoneuron activity revealed a rostrocaudally propagating component of the optical signal in the rostral lumbar and caudal segments (Bonnot *et al.*, 2002). Although, we also observed this pattern of activation in the rostral lumbar segments of the neonatal rat spinal cord (Falgairolle *et al.*, 2007), it remains unclear whether this is attributable to the specific involvement of the hindlimb CPG since at the rostral lumbar level, hindlimb motoneurons are co-localized with axial motoneurons (Falgairolle *et al.*, 2007). Indeed, the possibility arises that the lumbar segmental output may concomitantly reflect different sources of rhythmogenesis: the lumbar hindlimb generators themselves and the networks responsible for back muscle activation (Figure 3B).

3.8.3. Humans

Metachronal propagation is not only restricted to undulating or quadrupedal organisms. To gain insights into the spinal neuronal organization of humans, we have investigated back muscle activity during various motor tasks. Electromyographic recordings (Figure 4A) were performed at various trunk levels, and the analysis of changes occurring in burst amplitudes and phase relationships revealed a comparable temporal organization with other species during forward bipedal locomotion (83). As previously described, two bursts of activity occur in axial muscles during each locomotor cycle (Figure 4A), when the fore- and hindlimbs are active. To identify the origin of this double-burst activation of trunk musculature, and to see if the system may adapt to changing behavioral conditions, subjects were asked to perform different types of rhythmic behaviors: forward walking (FW), backward walking (BW), amble walking (where the subjects move their arms in phase with the ipsilateral leg), walking on hands and knees (HK) and walking on hands with the knees off the treadmill (Hand). The bursting pattern recorded under these conditions could be classified into three categories: (1) double-burst rhythmic activity in a descending (i.e., with a rostrocaudal propagation) motor wave during FW, BW and HK conditions; (2) double-burst rhythmic activity with a stationary motor wave (i.e., occurring in a single phase along the trunk) during the 'amble' walk condition; and, (3) monophasic rhythmic activity with an ascending (i.e., with a caudorostral propagation) motor wave during the Swing and Hands conditions. This strongly suggested that the erector spinae (ES) muscle activation, which was specific to the given motor task, was able to express considerable flexibility.

Another remarkable feature of back muscle EMG activity is the long delay required for motor wave propagation along the spinal cord. The phase lag value as well as its sign (ascending or descending) varied with the locomotor task and it may represent up to 17% of the ongoing locomotor cycle. This means that it takes about 180ms for the motor wave to propagate along the spinal cord. Long-lasting propagation (25% of a cycle from L2 to T3) was also observed in the isolated spinal cord of the newborn rat (75). If long projecting fibers that distribute the motor command to each segmental level were solely involved, propagation would presumably be faster if we consider the time taken for axonal spike conduction along the fibers added to synaptic relays (i.e. about 50ms total time). In humans, on the basis of a similar involvement of action potential conduction velocity and synaptic delay, propagation time along the entire spinal cord pathways should be less than 10ms. This suggests that in humans as well as in lampreys (78, 84) and in newborn rats (74, 75), the propagation of axial motor command is mediated by local circuit interactions between segmental spinal networks, as well as long coupling fibers.

Understanding the role of the metachronal activation of back muscles during walking, and the role of trunk muscles in the maintenance of dynamic postural equilibrium, requires, EMG recordings together with synchronized kinematics and dynamic data analyses. However, studying an activity such as walking presents a major drawback, since due to its cyclic nature, it is not possible to discriminate between anticipatory and reactive adjustments. Therefore, we compared trunk activity during both gait initiation and steady state walking in order to gain further insight into: 1) the role of back muscle activity in normal walking, and specifically, how these muscles contribute to driving trunk movement that facilitate lifting the pelvis and the leg; and 2) how trunk activity is programmed during a transition between postural and dynamical states at gait initiation. We found that in the frontal and horizontal planes, a latero-flexion and rotation occur before and after step initiation in the upper trunk and lower trunk, respectively. A comparison of back muscle EMGs and trunk kinematics (Figure 4B), showed a metachronal activation of the back muscles during the preparation of the first step for gait initiation as well as just before the double support phase during walking. Moreover, trunk muscle activity precedes corresponding kinematics activity, indicating that the back muscles drive trunk movement during locomotion, thereby facilitating pelvis mobilization. Our EMG data showed that back muscle activity anticipates propulsive phases in walking, suggesting an underlying programmed control by a spinal central pattern generator.

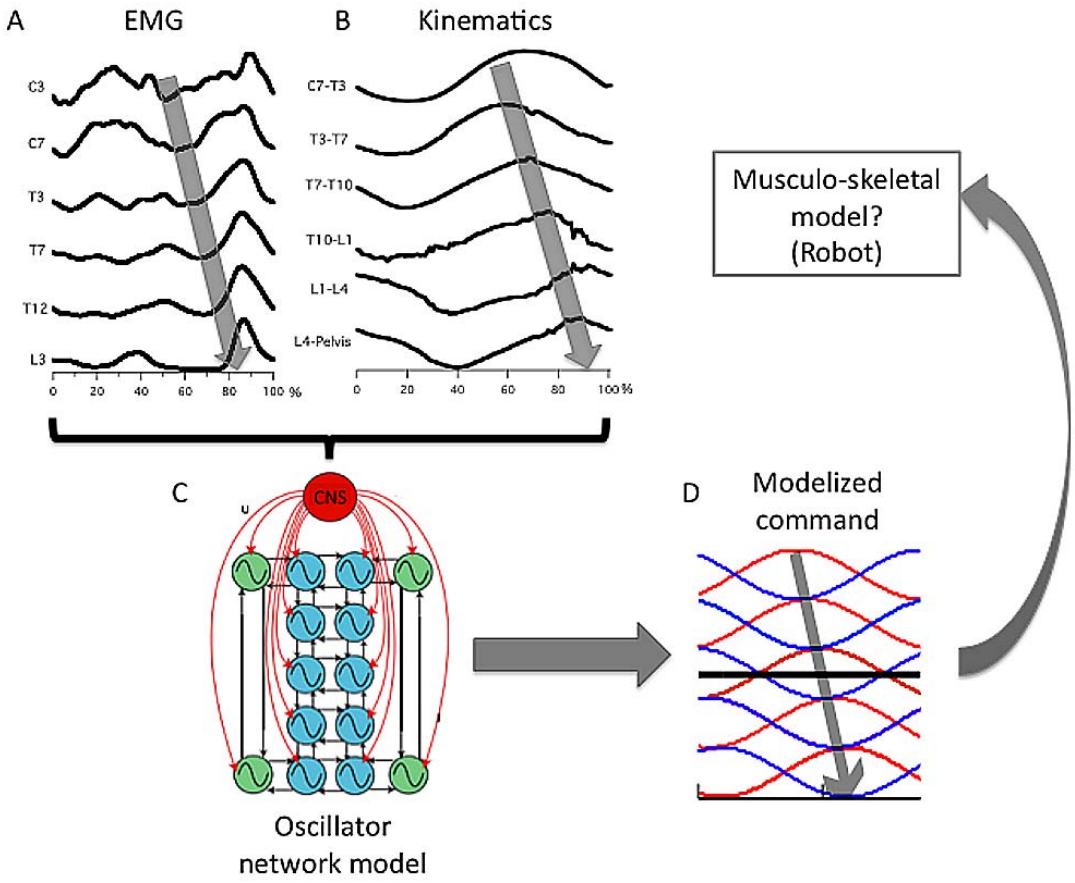

Figure 4. From the measured metachronal wave in human trunk toward the modeled command. (A) Electromyographic recording of Erector spinae muscles at various levels from C3 to L3 during human walking. The descending arrow shows the metachronal descending onsets of back muscles activities. (B) Inter-vertebral angles of the spine at various levels from C7 to the pelvis in the frontal plane. The intervertebral angle is the rotation (in the frontal plane) between two references attached to vertebral segments (for example between C7 and T3 segment for C7-T3). The descending arrow shows the metachronal descending inversion of spine curvature. (C) Structure of the oscillator network designed to produce a command for the EMG and kinematics observed activities. CNS: Central Nervous System. Five pairs of oscillators in column represent left and right side of five trunk segments. Four oscillators outside the column represent the limbs (2 arms above, 2 legs below). The curved arrow represents the general commands of the CNS. The straight arrow represents interaction between the different oscillators that will allow the expression of various synchronizations between each segment, metachronal descending wave being one of them. (D) Output of the oscillator network for the trunk oscillators expressing a metachronal descending wave (arrow) with opposite phase between left and right sides (sinusoids with opposite phases). The next step will be the use of this command in a musculoskeletal model.

4. MODELING STUDIES

Modeling studies have been performed to better understand the fundamental mechanisms that underlie metachronal propagation in the various systems described above. According to Marder and Abott (85) three general classes of model can be defined. Firstly, the speculative model, which supplies a formal exploration into the possible implications or the potential consequences of a biological process; it can also suggest a possible solution to an enigma or an inexplicable phenomenon. When developing such a model, the investigator often begins with a problem then he/she builds a possible solution, which in turn suggests new ways for actual experimentation. Secondly, integrative models exist, which are used to verify if a set of data is adequate to explain the behavior of a system. By nature, these models are closely connected with experimental data, with their most immediate purpose being to specify lacking data and to suggest ways to find them. As such, these models can be also used as speculative models. Thirdly, there are the interpretative models, which allow the integration, interpretation or categorization of data and offer new tools of data analysis.

All three types of model have been used to model metachronal propagation. An interesting feature throughout these models is the capacity for a module (cilia, ganglion, segment) to generate its own rhythmic activity. Therefore, coordination at the systems level becomes a problem of the mode of information distribution. However, a distinction

must occur between the cellular ciliary movements and the central nervous activities of invertebrates and vertebrates, since cilia operate independently one from the other in the absence of an underlying network that organizes their coordination.

4.1. Cilia

For cell cilia, therefore, a major aim is to understand how all the units bend in the same direction. Models involving hydrodynamics were generated for this the purpose (11, 86). The hypothesis is that the system does not precisely determine the beating of cilia to create a wave, but that the movement of individual cilia influences the movement of its neighbor and that this interaction produces the metachronal wave observed.

4.2. The central nervous system of invertebrates and vertebrates

The neural bases of intersegmental coordination have been studied with many theoretical models from biophysical models to much more abstract approaches. The theory developed by Cohen and Ermentrout (87) to understand intersegmental coordination is an excellent illustration of how a general theory can be developed for systems which share common properties, and adapted to account for their differences. This strategy was widely used for networks that can be considered as chains of oscillators. Invertebrate systems enter into this category because their nervous system is discrete and segmentally organized comprised of ganglia that have been often roughly considered as oscillating networks. The same approach cannot be directly applied to vertebrates, which present a continuous nervous system, without a strict anatomical segmentation (although the metamerisation observed at the spinal level approaches this). These systems have however been considered as a chain of oscillators since they present an intersegmental coupling (88). In all animal models so far studied, the metachronal distribution is thus based on a chain of oscillators connected in both directions with their closest neighbors (88). The properties of these theoretical networks have been modified from one biological system to another, in order to adapt each to the experimental data known for a given species. Two theories have emerged from these modeling studies (89): 1) a gradient of excitability in which the oscillator expressing the fastest intrinsic frequency imposes its own rhythm on the others; and 2) intersegmental connectivity in which the connections between the various oscillators are not identical, depending on the direction of propagation wave or their site (rostral or caudal part of the spinal cord) of location.

Distal connections have been also added to some models (90). These theoretical models have often been followed by cellular models, based on the known architecture of the system and the ionic channels involved, to understand the cellular mechanisms underlying distribution of activity.

4.2.1. Segmental models

4.2.1.1. Leech

Leech swimming was modeled by means of a chain of harmonic oscillators coupled through multiple connections (91). Surprisingly, activity was found to be initiated in the central ganglia and propagate rostrally and caudally from this point. An asymmetric bidirectional coupling with distal connections was also incorporated into the model as well as synaptic gradient. A more recent version of this model (Cang and Friesen, 2001) incorporates cellular parameters.

For crawling in the leech, two types of models have been proposed. First, a model (20) inspired by the kinematic characteristics of crawling to simulate the patterns of motoneuron activity along the nervous system. In this case, a single oscillator in the rostral part of the nervous system drives the elongation and a second oscillator drives the contraction in the first segment of the body. Each segment has its own motor controllers for elongation and contraction, which are driven, by their equivalent controllers in the more rostral segment. To produce an adequate motor output close to that recorded *in vivo*, the motor controllers require an excitatory input. This model derives principally from the kinematic data and recordings from motoneurons in semi-intact or whole preparations of the central nervous system.

A biomechanical model (92) explains how the motor patterns produce actual movement. It was built from the anatomy of the leech, the passive mechanical properties of the body, the contractile properties of muscles, and pressures measured in the lumen of the leech when it crawls and swims. The model incorporates three types of muscles: the longitudinal, circular and dorso-ventral. The model supposes that every segment maintains a constant volume with time and that the motoneurons uniquely drive muscles of their own segment.

4.2.1.2. Crayfish

The swimmeret system is considered as a chain of four oscillators coupled in a bidirectional manner with their immediate neighbors (93). The model's properties (Figure 1D) are as follow: 1) the coupling between segments is asymmetric since the ascending coupling delays the activity by about 25%, while the descending coupling advances the activity of the more caudal segment by 25%; 2) the ascending and descending couplings have the same strength; 3) the intersegmental coupling does not alter in a significant way the cycle period of the system; and 4) the level of excitation of the system changes the period of every oscillator, and can also change the properties of every intersegmental coupling.

The model differs from other segmental models in that it is unilateral. It also includes non-spiking neurons with graded synaptic transmission and the number of elements included in the model is extremely low.

4.2.1.3. Lamprey

The lamprey locomotor pattern has been extensively modeled to test hypotheses that could be checked experimentally. Various models, from abstract bilaterally coupled oscillators (87, 94) to highly realistic biophysically-inspired models (95-97) have been developed. The latter have enabled populations of neurons to be simulated, with every neuron modeled with subcategories of various ion channels (NA+, K+, Ca2+ and

KCa). In most cases, the neuron is subdivided into three different compartments (dendrites, soma, initial segment) and the properties of these neurons were adapted to mimic each category of experimentally identified spinal neuron.

The theoretical models were based on a chain of oscillators. Every oscillator represents a segment that produces the adequate motor output with the coupling between oscillators setting the intersegmental coordination. Each segment is considered as two bilateral (hemi-segmental) networks operating with reciprocal inhibition. They are connected along the spinal cord according to known coupling properties (98). These models are very simplified at the biological level to focus on their connections and their architecture.

4.2.1.4. *Xenopus*

Modeling of the *Xenopus* locomotor system has also tried to simulate the spinal oscillators involved in swimming. Studies have used a small number of models of realistic neurons to build minimal oscillators with mutual inhibition organizing the bilateral alternation of activity (64, 99, 100). To account for the characteristics of swimming activity as observed *in vitro*, modeling studies have defined three spinal zones with different properties. The first zone, located in the most rostral part of the cord, sustains the fundamental oscillators that are often referred to as segmental oscillators. These are silent during rest periods and need continuous excitement to be active. This excitation is supplied for each oscillator by a positive feedback on every cycle of swimming. When such an excitation is present, the segmental oscillators can generate a steady rhythm, alternating bilaterally, in response to a stimulus. This type of segmental oscillator, which does not require a phasic extrinsic excitation, allows modeling the most rostral spinal segments. The second zone was modeled with neuronal networks called potential oscillators. These include all components of a segmental oscillator, such as reciprocal inhibition, but their level of excitation is insufficient to generate an activity when they are isolated. The third zone does not possess any rhythmogenic property and responds passively to synaptic command. To date, the only study, which has been conducted on intersegmental coordination, modeled unidirectional coupling between segmental potential oscillators (101).

4.2.1.5. Salamander

Modeling studies in the salamander have been largely based on data obtained from the axial locomotor networks in the lamprey, with, however, changes introduced at the level of the pelvic and scapular girdles to include the limbs in the model (102-105). As previously mentioned, however, not enough information is available on the cellular organization of this network and so most modeling studies have relied on knowledge obtained in the lamprey. The challenge has been to model the salamander's two modes of locomotion, swimming during which the animal's limb are held backwards along the body to produce anguilliform locomotor movements, and walking which involves all four limbs. A recent model allowed simulating this bimodal behavior by robotics (105). This model was based on 4 hypotheses: i) the axial CPG has a similar basic design to the lamprey (chain of coupled oscillators, 106) ; ii) the limb oscillators have a slower frequency than the axial oscillators (105) ; iii) the isolated axial CPG generates spontaneously travelling waves ; and iv) the coupling from the limb CPGs to the axial CPG is stronger than the reverse (107). In addition, to take into account that walking requires a weaker MLR activation than swimming (73), the limb oscillators were assigned with a lower intrinsic frequency than those of the trunk. Altogether, this model assumes a phylogenetic preservation of the axial spinal neuronal networks; it reproduces very closely the actual locomotor behavior of the salamander.

4.2.1.6. Rodents and cats

The complexity of the neuronal networks in these mammals and the lack of data at the cellular level have limited modeling studies to partial representations of the underlying locomotor CPGs. Simulations have been based mostly on hindlimb walking and on the flexor/extensor relationship in particular. The CPGs are proposed to be organized in a coupled oscillator model in which inhibition is crucial for alternation, but not for rhythm generation (81, 108). Models have also described the activity of one segment in a disinhibited spinal cord (109). This study was based on a previous model established for the spontaneous locomotor-like activity recorded in chick embryo (110-112). This is a mean field model that describes the average firing rate of a population (motoneurons in one segment), but not the detailed electrical activity of individual cells. It also includes three variables: the population activity, a fast depression variable representing the fraction of synapses not affected by the fast synaptic depression, and a slow neuronal depression that underlies the onset and termination of episodes as well as the long silent phases.

Few modeling studies on mammal locomotion have shown or have considered the spinal propagation of activity (81, 113). Yakovenko *et al.* (113) created a model describing motoneuronal activity in the cat lumbosacral spinal cord. By targeting the limb muscles involved during locomotion and using used the known location of motoneurons pools innervating these muscles. They then used the known electromyographic activity of these muscles in the locomotor step cycle to compute the firing activity of their innervating motoneurons. The model then predicted that a rostrocaudal activity should be observed in the hindlimb motoneurons. In another study of for cat hindlimb activity, Perez *et al.* (81) created a model to describe the activity of dorsal interneurons during scratching. They built their model as a chain of CPGs, each consisting of a two level architecture, one responsible for generating the rhythm and the other for defining the actual motor output pattern. These CPGs were connected via excitatory synapses with their closest neighbors in the rostrocaudal direction. The two layers were connected through a direct asymmetric excitatory synapse and an interposed inhibitory interneuronal population. They were able to show that their model reproduces the motor activity recorded experimentally in control conditions as well as a rostrocaudal activation of the interneurons.

4.2.1.7. Human

Some models of CPGs have been developed to simulate human movement, although they have focused mainly on limb control (114-117) and not specifically on trunk control. As seen above, however, the pattern of back muscle activation during human walking is comparable to that observed in other vertebrates or invertebrates (see above), for which much data are available on the cellular organization of neuronal networks underlying this behavior. It is therefore tempting to model a human CPG that would reproduce the trunk metachronal descending wave according to the operational dynamics of the axial locomotor network. Based on this assumption, we have recently proposed to adapt an existing system of coupled non-linear oscillator networks (105) to mimic human locomotion and in particular to replicate the trunk descending muscular pattern observed during normal gait (Figure 4C). In order to reproduce movement of valid limb and integrate voluntary control of the rest of the body, we have developed a model that has to be adaptable to different voluntary controlled modes of locomotion as well as to the influence of external conditions and proprioceptive information. On this basis, therefore, such a model must have two levels of control, "voluntary control" which represents the high decision-making level for walking, running, going faster, and "adaptive control" which represents the automatic adaptations to the external conditions such as ascending slope, descending slope and terrain texture.

The CPG model developed was again based on coupled non-linear oscillator networks (104, 105). It produces traveling waves as limit cycle behavior (Figure 4D), and allows a simple modulation of the frequency, amplitude and phase lag of undulations. Using real recorded information from a unique sensor placed on the upper body, we have shown that the model was adaptable to different voluntarily controlled modes of locomotion as well as to the influence of external conditions and proprioceptive feedback information.

4.2.2. Continuous model

Most of the models of vertebrates make the hypothesis that the spinal cord is comparable to a ganglionic nervous system, thereby considering a continuous system as a discrete one. Hence, distinctions were made between intra-segmental and inter-segmental connections, although, to date, it has been rather difficult to link this view to anatomical reality in either *Xenopus* or lamprey. Dale (118) reported that it was possible to create a model which could reproduce the rostrocaudal coordination observed during *Xenopus* swimming without recourse to coupled oscillator theory. Indeed, this behavior was reproduced by a network of neurons randomly connected according to a minimum of rules (axon size, probability of synapse formation). In the lamprey, it has also been shown that the metachronal propagation could be generated by structures other than a chain of coupled oscillators (119). To achieve it, these authors modeled two cell types, the excitatory and crossed inhibitory interneurons that constitute the CPG. Ipsilateral interneurons with long descending axons were also added. Neurons assumed to be motoneurons and representing the sum of excitatory and inhibitory inputs from interneurons, were also modeled. This model produced simulations very close to the activity patterns observed *in vitro*. According to Grillner and Wallen (84), their results suggested that the representation of the metachronal propagation of rhythmic locomotor activity in the lamprey by a series of coupled oscillators could be an oversimplification.

5. IS THERE A PHYLOGENETIC PRESERVATION OF METACHRONAL WAVE PROPAGATION MECHANISMS IN MAMMALS?

We have reviewed here a variety of systems, from unicellular organisms to humans, in which motor patterning is organized according to a sequential activation of modules (metachronal propagation) that in turn ensures organism displacement. A combination of neurobiological and modeling studies has supported the hypothesis that the principles of functioning and the basic design of neuronal circuits have been conserved during evolution.

Locomotor activities recorded in mammals, including humans or quadrupeds, have the common feature of a segmental distribution along the spinal cord. This motor wave, responsible for the rhythmic curvature of the trunk, is essential for step production and the fluency of stepping, as well as the preservation of balance during locomotion. As seen above, one characteristic of this motor pattern is its ubiquity, since it has also been observed in most animal models that exhibit an eel-like swimming strategy: the leech (120), lamprey (77, 78, 84, 121) and tadpole (60, 101, 122).

By considering the onset of the human bipedal locomotion to result from an evolutionary continuum emerging from undulatory swimming, one can ask as to what extent traces of primitive spinal structures have been preserved in mammals. The structures responsible for the motor wave observed in the lamprey and the tadpole were described as being networks of segmental oscillators interconnected by local connections (78, 101). Moreover, the appearance of the limbs necessarily modified these structures. The salamander is a mixed model since two modes of locomotion can be performed independently one from the other. This allowed determining the influence of both scapular and pelvic girdles on the axial network activity, even when the limbs are not actively involved in locomotion, and their predominant role during the walking (66). The presence of a stationary wave or a metachronal one was reported in various studies during the two modes of locomotion (66, 123). In the rat, we found that the local axial networks are capable of producing rhythmic activity independently of the limb CPGs. However, this axial activity is intrinsically related to limb activity since the rat does not produce undulatory swimming (124). Like in lower vertebrates, the presence of long propriospinal fibers involved in locomotion was revealed (74). Moreover, the kinetics of motor activity propagation (a delay of several 100ms along the body) suggests that strong local interactions are additionally involved.

The direction of propagation in the rat, both *in vitro* and *in vivo* (see above), is caudorostral in contrast to what is observed during forward locomotion in the lamprey (38) or humans (125). The electrophysiological data obtained, show that the lumbar CPGs exerts a dominating influence on all the spinal structures involved in locomotion (126). Since the adult rat mainly uses its hindlimbs to propel itself, it could be argued that this determines the direction of the motor wave. However, our data show that in humans, where the lower limbs are also the effectors for propulsion, the expression of the underlying motor pattern is extremely flexible, since both the intersegmental delay and its direction can be modified.

In humans, the existence of lumbar CPGs for leg movements but also of cervical CPGs for arm movements has led to the suggestion that the transition to bipedalism did not dramatically reconfigure the overall neuronal organization (127-129). Therefore, in light of our data obtained in humans, i.e. that a sequential distribution of the axial motor activity is present during walking, it also seems reasonable to suggest that segmental oscillators are present, although direct evidence to support this notion is still unavailable. Obtaining such evidence will require the development of experimental protocols in connection with clinical research, as were successfully done to reveal the existence of the lumbar CPGs (127, 130, 131) on hemiplegic or paraplegic patients.

6. CONCLUSION

The phylogenic comparison of axial neuronal network functioning suggests that despite dramatic changes undergone by the human muscular and skeletal systems during the switch from quadrupedal to bipedal walking and erect posture, common mechanisms for trunk control may be shared throughout vertebrates. Although most of the studies reported in this review deal with motor systems, traveling electrical waves are also observed across olfactory, visual, and visuomotor cortical areas in a variety of species (132). Therefore, studying the organization of neuronal networks with a clear definable behavioral relevance, such as those involved in motor activity, may help in understanding the functioning of other brain structures, and the theory of coupled phase oscillators may provide a general framework for unveiling the coordinated functioning of a variety of networks of neuronal oscillators.

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