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Review Article

Mechanisms of Locomotion

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Abstract

The activity pattern of various limb muscles during locomotion is primarily determined by the operation of the spinal generator. The flexor and extensor half-centers activate corresponding motoneurons of flexor and extensor muscles. It can be assumed that motoneurons of biarticular muscles receive activating inputs from both half-centers, but a stronger influence from the flexor half-center, which explains their predominant activity during the flexion phase at low locomotion intensity. As for the motoneurons of the extensor digitorum brevis and extensor digiti quinti, their connection to the half-centers is likely organized in a more complex manner. During locomotion in mesencephalic cats, as expected, individual α-motoneurons generate bursts of impulses in one movement phase and remain inactive in the other. In steady-state locomotion, the average inter-spike interval within a burst range from 25 to 40 ms. Only at the beginning or end of a motor episode can this interval increase.

Keywords: locomotion; spinal generator; motoneurons

Introduction

Locomotion in a broad sense is understood as a set of coordinated movements by means of which animals actively move in space. In four-legged mammals, for example, various types of locomotion are observed: walking, running, galloping, jumping, climbing, crawling, swimming, and others [1].

During locomotion, the central nervous system of the animal is faced with the need to solve the following main tasks:

1. Selection of the type of locomotion depending on the purpose of the animal's movement [2].
2. Organization of stereotypical movements of limbs and other body parts characteristic of the selected type of locomotion [3].
3. Adapting movements to external conditions.
4. Maintaining posture and balance during locomotion.

In this article, the nervous control of rhythmic limb movements during terrestrial locomotion of four-legged mammals (cats, dogs, rabbits), mainly during walking and running, will be considered, i.e. some mechanisms of the nervous system's solution of the second and third tasks will be touched upon. Therefore, in the following, the term locomotion will be used in a narrower sense - to denote coordinated stereotyped movements of the limbs during walking and running. Information on the kinematics of locomotor movements of the limbs in vertebrates and on the activity of various muscles underlying these movements can be found in literature reviews by Grillner, Schick, and Orlovsky. They also review the neural mechanisms of vertebrate locomotion. Stein's review analyzes numerous data on the neural control of locomotion not only in vertebrates but also in invertebrates. To facilitate consideration of the mechanisms of neural control of locomotion, the general scheme of the organization of the control system of these movements will be outlined first, followed by the mechanisms of functioning of its individual links. In this article, the nervous control of rhythmic limb movements during terrestrial locomotion of four-legged mammals (cats, dogs, rabbits), mainly during walking and running, will be considered, i.e. some mechanisms of the nervous system's solution of the second and third tasks will be touched upon. Therefore, in the following, the term locomotion will be used in a narrower sense - to denote coordinated stereotyped movements of the limbs during walking and running. Information on the kinematics of locomotor movements of the limbs in vertebrates and on the activity of various muscles underlying these movements can be found in literature reviews by Grillner, Schick, and Orlovsky. They also review the neural mechanisms of vertebrate locomotion. Stein's review analyzes numerous data on the neural control of locomotion not only in vertebrates but also in invertebrates.

To facilitate consideration of the mechanisms of neural control of locomotion, the general scheme of the organization of the control system of these movements will be outlined first, followed by the mechanisms of functioning of its individual links.

Currently, the control system for locomotor movements is presented as follows:

- Each limb is controlled by its spinal generator [4], which can alternately activate flexor and extensor motoneurons even in the absence of cyclic afferent or descending impulse flow.
- Activation of the spinal generator (the transition from the resting state to the generating mode) is accomplished by specific descending command neurons [5]. Signals from them are organized relatively simply and represent a tonic flow of impulses.
- The intensity of the tonic descending stream, the frequency of impulses and the number of active command neurons determine the level of activation of the generator. In turn, the intensity and frequency of locomotor movements depend on the level of activation: a higher level of activation corresponds to a higher intensity and frequency of locomotion [6].
- Inter-endothelial coordination is based on the interaction of generators, which is realized with the help of coordinating neurons. The type of interaction (antiphasic or in-phase), as well as the operation of individual generators, is determined by the intensity of tonic downward flow.
- Spinal locomotor automatism is subject to a powerful corrective influence from peripheral afferents and fast-conducting descending systems. Impulsation coming through afferent inputs and fast-conducting descending fibers contains a phase component and affects both oscillator neurons and motoneurons, which makes it possible to effectively change not only the phase and amplitude of limb movement, but also the activity of individual muscles.
- Modulatory influence on the work of the fast-conducting descending systems is exerted by various brain structures, primarily the cerebellum. These structures receive information about limb movement and activity of spinal locomotor centers, forming corrective signals transmitted to spinal centers.
- On the basis of this concept, the neural mechanisms of locomotion will be further considered.

Tonic Control of Spinal Locomotor Centers

Decorticate, thalamic, and hypothalamic animals (with the caudal hypothalamus preserved) demonstrate the ability for spontaneous locomotion in acute experiments. Intact animals under light anesthesia also exhibit spontaneous locomotor activity. However, decerebrated cats, in which the caudal hypothalamus remains rostral to the transection site, are incapable of spontaneous locomotion in acute experiments. Voluntary locomotion is also impossible in non-anesthetized cats with lesioned caudal hypothalamus, though this ability recovers after several weeks.

In chronic experiments, mesencephalic cats (with brainstem transection extending from the anterior edge of the superior colliculi to the posterior border of the mammillary bodies) and animals with intercollicular decerebration also show restored spontaneous locomotion [7]. Animals with transections at lower levels display no spontaneous locomotor activity in either acute or chronic phases [8]. These experiments indicate that structures in the caudal hypothalamus and midbrain play a key role in initiating and maintaining locomotion [9]. Electrical stimulation experiments of various brainstem regions have further localized the structures responsible for activating the spinal locomotor generator. Tonic stimulation of the *nucleus subtalamicus* in intact and decerebrated animals was found to elicit locomotor movements. This region was termed the hypothalamic locomotor region (HLR).

In acute experiments, electrical stimulation of an area ventral to the inferior colliculi—approximately corresponding to the *nucleus cuneiformis*—induces locomotor movements in mesencephalic cats. In intact cats with lesioned HLR, stimulation of this mesencephalic locomotor region (MLR) also triggers locomotion. In thalamic cats, MLR lesions do not prevent spontaneous or HLR-stimulated locomotion, though their spontaneous motor activity is significantly reduced. The optimal stimulation frequency for evoking locomotion is 30–60 Hz. Increasing current intensity results in more vigorous locomotion, even transitioning from walking to galloping.

However, HLR and MLR are not functionally equivalent. Animals with intact HLR exhibit spontaneous locomotion, and after immobilization, rhythmic activity is recorded in motor nerves (**fictive locomotion**). In the absence of HLR (e.g., in mesencephalic cats during acute experiments), spontaneous locomotion does not occur—movement is only elicited by MLR stimulation, and no fictive locomotion is observed.

The functional distinctions between HLR and MLR are further evident in stimulation experiments on hypothalamic cats:

- HLR stimulation invariably triggers locomotion.
- MLR stimulation is only effective *during* spontaneous or HLR-induced locomotion, enhancing its intensity.

The underlying mechanisms remain incompletely understood. A partial explanation lies in the stronger tonic descending drive in thalamic animals compared to mesencephalic cats, which provides greater activation of spinal locomotor centers.

Alternative Locomotion Pathways In mesencephalic cats, locomotion can also be elicited by stimulating pyramidal tract fibers at the pontine level (provided the bulbar pyramids are transected beforehand). Notably, lesioning the most effective part of the MLR in such cases does *not* prevent locomotion. These findings suggest that the pyramidal tract, HLR, and MLR are facultative for locomotion: disabling any two of them still allows locomotion to be evoked by stimulating the third. Moreover, their effects are additive.

Locomotor activity can also be induced by:

- Lateral regions of the pons and medulla in mesencephalic cats.
- Caudal ventral pons, which facilitates MLR-stimulated locomotion.

The "Locomotor Strip"

Microstimulation studies revealed that in cats, the MLR extends caudally as a locomotor strip, reaching the C1 spinal segment. Stimulation of this strip (10–15 μA current) evokes locomotion.

- In the medulla, it lies ventral to the spinal trigeminal nucleus.
- At C1, it coincides with the Rothmann-Sherrington point, whose stimulation produces stepping movements in decerebrate cats.

The strip's trajectory does not fully overlap with any known descending tract. It is likely associated with the locus coeruleus (*n. coeruleus*), whose noradrenergic neurons project to the spinal cord.

Synaptic Mechanisms

MLR stimulation induces transsynaptic activation of other descending systems. For example, reticulospinal neurons can be monosynaptically

activated by MLR stimulation. The critical role of MLR's synaptic connections is underscored by experiments where a brainstem transection at A-2 (Horsley-Clarke coordinates) — sparing the MLR itself — *completely blocks* locomotion. This implies that structures *rostral* to the MLR are essential for initiating locomotion in mesencephalic cats.

Direct Hypothalamospinal Pathway

Kuypers and Maisky discovered a direct descending pathway from the caudal hypothalamus to the spinal cord, originating in the *zona incerta*. Given its proximity to HLR, this tract may mediate spinal locomotor activation during HLR stimulation. Integrated Network Activation Stimulation of both HLR and the transected bulbar pyramids triggers transsynaptic activation of brainstem descending systems. This aligns with known extensive connections between:

- Caudal hypothalamic structures,
- Corticofugal fibers, and
- Midbrain, pontine, and medullary nuclei.

Supporting evidence includes monosynaptic activation of pontomedullary reticulospinal neurons during HLR stimulation.

Thus, the corticofugal tract, hypothalamic locomotor region (HLR), and mesencephalic locomotor region (MLR) should be considered input nodes for descending systems that directly activate spinal locomotor centers. According to a widely accepted (though not yet definitively proven) hypothesis, these descending systems are **monoaminergic tracts**—supported by extensive indirect evidence.

Monoaminergic Systems and Spinal Locomotion

The cell bodies of monoaminergic neurons are located in the brainstem (pons and medulla), with their axons projecting to the spinal cord. To simulate their physiological effects, animals are typically administered precursors of norepinephrine (NE) and serotonin (5-HT) synthesis, which are believed to increase neurotransmitter release from monoaminergic terminals.

- Spinal cats in acute experiments are incapable of locomotion, but L-DOPA (L-dihydroxyphenylalanine) administration effectively activates their spinal locomotor centers.
- These animals begin performing stepping movements on a treadmill.
- After immobilization, rhythmic activity in motor nerves (fictive locomotion) is recorded.

- L-DOPA induces a characteristic reorganization of spinal reflexes, similar to that observed in:

1) Hypothalamic animals with spontaneous locomotion,

2) Mesencephalic animals during MLR stimulation.

Pharmacological Modulation of Locomotion

- Pyrogallol (a COMT inhibitor, blocking NE degradation):
- Induces prolonged fictive locomotion in immobilized hypothalamic cats.
- Triggers spontaneous stepping in mesencephalic animals without MLR stimulation.
- Potentiates MLR stimulation effects.

- NE receptor blockers:

- Attenuate L-DOPA effects and inhibit MLR-induced locomotion.
- Other locomotor-activating agents:
- Clonidine (direct α-adrenoreceptor agonist).
- Amphetamine (indirect sympathomimetic).

- 5-HTP (5-hydroxytryptophan, a serotonin precursor):

- Reorganizes spinal reflexes similarly to L-DOPA.
- Induces fictive locomotion in spinal rabbits**—but **not in cats.
- Effects are blocked by serotonin receptor antagonists.
- Synergistic effects:
- Combined administration of L-DOPA or 5-HTP with MAO inhibitors (preventing NE/5-HT breakdown) enhances locomotor activation.
- Norepinephrine vs. Serotonin in Locomotor Control

While there is strong evidence that noradrenergic (and likely serotonergic) descending systems activate spinal locomotor centers during locomotion, the primary role of NE has been questioned:

- Jordan and Steeves demonstrated that NE is not the sole mediator:
- After chemical destruction of noradrenergic fibers (via 6-hydroxydopamine), NE levels in lumbar segments dropped 5-fold, yet hindlimb locomotion remained largely intact.
- Even after decerebration, MLR stimulation still evoked locomotion, with movement initiation (as in mesencephalic cats) beginning in the hindlimbs.

The data suggest that:

- HLR, MLR, and corticofugal pathways converge on monoaminergic descending systems to drive spinal locomotion.
- NE is sufficient but not strictly necessary for locomotion, implying compensatory mechanisms (e.g., serotonin or other neuromodulators).
- Species differences exist (e.g., 5-HTP's efficacy in rabbits but not cats).

This aligns with the view that multiple parallel pathways ensure robust locomotor control, with redundancy in neuromodulatory activation.

Interestingly, L-DOPA enhances rhythmic discharges in extensor nerves while reducing their amplitude in flexor nerves in immobilized, lightly anesthetized rabbits. In contrast, 5-HTP exerts the opposite effect. This suggests that:

- Noradrenergic systems predominantly activate spinal extensor centers.
- Serotonergic systems primarily facilitate flexor-related spinal circuits.

Potential Role of Fast-Conducting Descending Pathways

The contribution of tonic activation in fast-conducting descending systems (e.g., **rubro-, vestibulo-, and reticulospinal tracts**) cannot be ruled out, as their activity increases during locomotion. Notably:

- The dorsolateral reticulospinal system (comprising thin myelinated fibers) elicits effects similar to L-DOPA and 5-HTP.
- Key difference: Unlike monoaminergic agents, its activation does not induce late, prolonged discharges in motor nerves upon stimulation of group II afferents.

Spinal Mechanisms of Monoaminergic Action

The precise spinal mechanisms remain unclear:

- Microapplication studies: Norepinephrine (NE) exerts inhibitory effects on select spinal neurons, suggesting it may tonically suppress locomotor generator activity.
- Current hypothesis:
- Locomotor rhythm generation is tonically inhibited by spinal "command neurons."
- Monoaminergic systems disinhibit the generator by suppressing these inhibitory interneurons, thereby enabling locomotion.

Plasticity in Chronic Spinal Animals

A comparable disinhibition mechanism may operate in chronic spinal animals:

- Within days post-transection, they regain the ability to perform stepping movements in response to exteroceptive stimuli (mechanism unresolved).
- Afferent Modulation of Locomotor Centers

Spinal locomotor centers are also strongly influenced by nonspecific afferent inputs:

- Classic observation (Sherrington):
- Noxious perianal stimulation can evoke unstable locomotion in acute spinal cats.
- Later studies identified increased locomotor center activity during stimulation of:
- Peripheral nerves,
- Dorsal roots,
- Dorsal columns.

Summary of Key Findings

- NE vs. 5-HT: Antagonistic modulation of extensor/flexor networks.
- Fast-conducting pathways: Complement monoaminergic control but lack late discharge effects.
- Disinhibition model: Monoamines release the locomotor generator from tonic inhibition.
- Afferent integration: Nociceptive and proprioceptive inputs can override or potentiate central locomotor commands.

Activating and Inhibitory Control of Locomotion

Potentiation of Locomotor Rhythm by Afferent Inputs

The most pronounced activating effects arise from stimulation of thin, high-threshold afferents [10]. These nonspecific afferent inputs exhibit effective **summation with descending monoaminergic activation:**

In both decerebrated and spinal animals (after L-DOPA administration), nonspecific peripheral stimulation increases the intensity and frequency of the locomotor rhythm [11].

Proposed mechanisms:

Primary hypothesis: Afferent input, like descending monoaminergic fibers, may inhibit inhibitory spinal interneurons, indirectly disinhibiting the locomotor generator.

Alternative: Direct excitatory effects on generator neurons cannot be ruled out [12].

Termination of Locomotion: Known Inhibitory Mechanisms

For effective locomotor control, the system must initiate, sustain, and halt movement. However, data on locomotion suppression remain sparse.

Documented inhibitory methods include:

Mechanical pressure on the dorsolumbar/sacral region.

Low-frequency (3–4 Hz) photic stimulation in lightly anesthetized, immobilized intact rabbits (suppresses rhythmic motor nerve discharges).

Stimulation of specific pontomedullary areas during MLR-induced locomotion.

Thalamic Modulation of Locomotion

Grossman's findings:

Stimulation of nonspecific thalamic nuclei inhibits HLR-induced locomotion without causing atonia or spasticity, suggesting a locomotion-specific inhibitory pathway.

Critical Knowledge Gaps

While progress has been made in understanding locomotor initiation, the mechanisms underlying its precise termination require urgent investigation.

Key questions:

How do pontomedullary and thalamic inhibitory signals integrate with spinal circuits?

Do afferent and descending inhibitory pathways converge on shared spinal interneurons?

Spinal Locomotor Generator Of A Single Limb: Organization Of Motor Output

1. Brown's Hypothesis and Basic Organization

The spinal locomotor generator is conceptualized based on Brown's hypothesis [13], which proposes that:

- Each limb is controlled by a single central pattern generator (CPG) composed of two half-centers (flexor and extensor).
- These half-centers alternate activation during locomotion, producing rhythmic movement.

2. Central Locomotor Program in Fictive Locomotion

Studies in immobilized thalamic cats during fictive locomotion reveal [14]:

- Temporal organization of efferent activity in nerves innervating hindlimb muscles supports Brown's hypothesis.
- Simplicity in most muscles:
- Basic alternation between flexor and extensor nerve activity.
- Variability:
- Fluctuations in intensity, duration, and phase-specific activity (flexion/extension) across step cycles.
- Implies critical roles for:
- Segmental reflexes (fine-tuning).
- Supraspinal corrections (higher-order modulation).

3. Afferent Modulation in Intact and Mesencephalic Cats

- Intact cats: Afferent input causes predictable reduction in extensor muscle activity early in the stance phase [15].
- Mesencephalic cats: More complex flexor/extensor patterns during evoked locomotion, likely due to disrupted supraspinal control.

4. Intensity vs. Frequency Dissociation

- Increased fictive locomotion intensity does not always raise step-cycle frequency.

- Explanation:

  - Higher speed initially requires stronger muscle activation (faster flexion/extension).
  - Frequency modulation depends secondarily on afferent feedback.

5. Complex Activation Patterns in Multiarticular Muscles

Muscles with dual functions (e.g., m. semitendinosus, m. peroneus tertius) exhibit intensity-dependent programming:

  - Low-intensity locomotion:
  - Activity only in early flexion phase.

- High-intensity locomotion:

  - Stronger, prolonged flexion-phase activity.
  - Additional (weaker) extension-phase bursts.

6. Digit Flexors: Phase-Shifting Activation

- Extensor digitorum brevis & digiti quinti (physiological digit flexors):

  - Dual-phase activity (flexion + extension).
  - Low intensity: Maximal during entire extension phase.
  - Medium/high intensity: Peak shifts to late flexion/early extension.

7. Consistency Across Preparations

Patterns observed in fictive locomotion align with data from:

  - Intact, decorticated, and mesencephalic cats (**with preserved afferentation**).
  - Confirms spinal CPG's robustness despite supraspinal or afferent perturbations.

Thus, the activity pattern of various limb muscles during locomotion is primarily determined by the operation of the spinal generator. The flexor and extensor half-centers activate corresponding motoneurons of flexor and extensor muscles. It can be assumed that motoneurons of biarticular muscles receive activating inputs from both half-centers, but a stronger influence from the flexor half-center, which explains their predominant activity during the flexion phase at low locomotion intensity. As for the motoneurons of the extensor digitorum brevis and extensor digiti quinti, their connection to the half-centers is likely organized in a more complex manner. During locomotion in mesencephalic cats, as expected, individual α-motoneurons generate bursts of impulses in one movement phase and remain inactive in the other. In steady-state locomotion, the average inter-spike interval within a burst range from 25 to 40 ms. Only at the beginning or end of a motor episode can this interval increase. The average inter-spike interval characteristic of a given neuron shows little dependence on locomotion intensity. An increase in movement intensity is primarily accompanied by the recruitment of new motoneurons. Further studies have revealed that the impulse burst of an individual motoneuron usually begins with one or two short inter-spike intervals (≤10 ms), followed by impulses with intervals of 25-40 ms.With an increase in the locomotor rhythm frequency, a shortening of the impulse burst is observed, but the described structure of inter-spike intervals is preserved. Stimulation of individual motor axons has shown that the maximum tension developed by a motor unit is achieved precisely with this structure of inter-spike intervals in the stimulating series. Moreover, the magnitude of the developed tension does not depend on the duration of the stimulating series. Thus, the initial high-frequency discharges ensure rapid tension development, while subsequent ones maintain it at a constant level. This organization of motoneuron discharge is likely particularly important during fast locomotion, when the extension phase lasts only 65 ms. An analogous discharge pattern of motoneurons is also observed during fictive locomotion in spinal animals. This indicates that the described activity characteristics of motoneurons are independent of afferent influences and are likely associated with specific features of the impulse patterns generated by the central pattern generator neurons. However, it cannot be ruled out that recurrent inhibition mechanisms or intrinsic properties of motoneurons may also contribute to the formation of such discharge patterns.

Numerous studies have demonstrated α-γ coactivation during locomotion - the simultaneous activation of α-motoneurons and homonymous γ-motoneurons. During spontaneous locomotion in decorticated cats, γ-activation typically precedes α-activation. In cases of limb deafferentation, γ-activation can occur even in the absence of α-activation, indicating that γ-motoneurons are more sensitive to central commands compared to α-motoneurons.

Fusimotor activation involves both static and dynamic γ-motoneurons. However, the ratio of static to dynamic γ-motoneuron activation differs between flexor and extensor muscles. In flexor muscles, the static effect of γ-motoneurons on muscle spindle sensory endings predominates and masks the dynamic effect. In extensor muscles, along with the static effect, a pronounced dynamic action is observed. In terms of impulse activity patterns, γ-motoneurons differ significantly from α-motoneurons. During locomotion in decorticated, mesencephalic, and spinal cats, the discharge frequency of γ-motoneurons shows strong dependence on movement intensity: higher locomotion intensity corresponds to higher discharge frequencies. This in turn leads to increased firing rates of muscle spindle afferents. Although α-motoneurons have a mechanism of recurrent inhibition, its role and dynamics (tonic and phasic changes) during locomotion remain incompletely understood. It is known that:

1) Administration of DOPA to spinal cats enhances recurrent inhibition of α-motoneurons [16].
2) In spinal cats after DOPA administration, stimulation of group Ia afferents (Ia afferents) induces:

1. prolonged (>250 ms) suppression of recurrent IPSPs in extensor motoneurons;
2. inhibition of Renshaw cell responses to ventral root stimulation.

3) During locomotion in mesencephalic cats, recurrent inhibition of α-motoneurons is suppressed, and this suppression begins already during passive limb movements [17].

Although the reflex action of Ia afferents weakens during activation of spinal locomotor centers, it can be assumed that afferent input plays a key role in suppressing recurrent inhibition: in spinal cats after DOPA administration; during locomotion in mesencephalic animals.

This is supported by data showing that:

1) Renshaw cell discharges are effectively inhibited during natural skin stimulation; during bursts of Ia afferent impulses.
2) During fictive locomotion in thalamic cats (when phasic afferent input is eliminated by immobilization), Renshaw cell excitability does not differ from the resting state; it does not depend on the phase of the step cycle.

Most Renshaw cells exhibit burst activity during fictive locomotion: bursts occur in a specific phase of locomotion at a frequency of 5–15 imp/s; in the opposite phase, the neurons are inactive.

Studies of recurrent IPSPs in motoneurons have shown that during fictive locomotion, phasic inhibition of Renshaw cells is absent; the observed

fluctuations in IPSP amplitudes may be associated with changes in membrane potential during periodic burst activity of motoneurons.

Thus, during fictive locomotion in thalamic cats, the efficacy of recurrent inhibition of α-motoneurons remains unchanged. However, the question of possible tonic changes in the efficacy of recurrent inhibition in thalamic animals compared to spinal ones remains open [18]. It is known that γ-motoneurons also undergo recurrent inhibition from Renshaw cells. This phenomenon has been described in spinal cats after DOPA administration. However, there is a lack of data in the literature: on changes in the efficacy of recurrent inhibition of γ-motoneurons following DOPA administration; on its dynamics during locomotion. The question of modulation of recurrent inhibition in Ia interneurons during locomotion also remains unresolved. Feldman and Orlovsky, in studies on four Ia interneurons in mesencephalic cats, found that:

1. in two neurons, the efficacy of recurrent inhibition decreased during locomotion;
2. in the other two, it remained unchanged.

These data suggest possible selectivity in the modulation of recurrent inhibition across different neuronal populations during motor activity.

1. Membrane Potentials of Motoneurons During Locomotion

Intracellular recordings of α-motoneuron activity during fictive locomotion revealed:

1. Cyclic fluctuations of membrane potential with alternating depolarization and hyperpolarization
2. Hyperpolarization represents an active IPSP process, confirmed by changes during hyperpolarizing/depolarizing current injection and responses to intracellular chloride ion administration.

In spinal animals after DOPA administration:

1. Extensor motoneurons exhibit hyperpolarizing shifts in membrane potential (IPSPs) during late bursts in flexor nerves
2. These IPSPs are primarily mediated by Ia interneurons, as ventral root stimulation almost completely abolishes hyperpolarization within 50 ms, and the IPSP amplitude depends on membrane potential [19].

2. Role of Renshaw Cells in Locomotor Switching

The obtained data suggest that phasic activity of Renshaw cells may participate in switching between flexor and extensor motoneurons. This is supported by the ability of ventral root stimulation to induce a switch from flexor to extensor activity [20].

3. Evolution of Brown's Hypothesis

The original concept by Brown proposed:

- The locomotor generator for each limb consists of two mutually inhibitory half-centers (flexor and extensor)
- Switching between half-centers is due to their fatigue
- The neuronal composition of the half-centers was not specified

Further developments:

- Three groups of interneurons were identified in the lateral intermediate zone and ventral horns:
    - Group I: activated by ipsilateral Ia afferents, inhibited by contralateral ones
    - Group II: opposite activation pattern
    - Group III: late activation from both sides

- Interneurons of Groups I and II were identified as Brown's half-centers

- Proposed organization:
    - Mutual inhibition between half-centers
    - Positive feedback within each half-center
    - Group III may participate in presynaptic depolarization of afferents [21].

4. Modern Views on the Neural Organization of the Generator

Subsequent studies confirmed and expanded these concepts:

- During real (mesencephalic cats) and fictive locomotion (spinal and thalamic cats), the following were identified:
    - Rhythmically modulated interneurons
    - Tonically activated/inhibited neurons
    - Indifferent interneurons

- Main groups of rhythmic interneurons:
    - C-neurons (active during flexion phase)
    - R-neurons (active during extension phase)
    - CR-neurons (mixed activity)
    - Ta-neurons (tonic activation)

Key features:

- The timing of interneuron activation does not always strictly correlate with step cycle phases
- Spatial overlap of different interneuron types in the gray matter
- Complex integration of rhythmic and tonic activity components

These findings support the concept of a distributed interneuron network as the basis of the spinal locomotor generator, where activity coordination is ensured by complex interactions between different neuronal populations.

1. Topographic Distribution of Rhythmically Active Interneurons

Studies have revealed that neurons altering their activity during fictive or real (after deafferentation) locomotion are predominantly localized in the same spinal cord regions where Jankowska et al. previously identified interneurons responding to late discharges upon stimulation of group I afferents (Ia afferents). Key observations:

- Interneurons activated during fictive locomotion typically also respond to induced late discharges [22]
- Correlation patterns between interneuron activity and efferent discharges are similar in both states
- The main difference: more pronounced modulation of impulse activity during fictive locomotion compared to late discharges
- These data suggest that late discharges can be considered a weakened form of locomotor rhythm.

2. Principles of Afferent Input Organization

- A clear relationship has been found between an interneuron's affiliation with a specific half-center and the organization of its afferent inputs:
    - Ia Interneurons
- Flexor half-center: receive inputs from Ia afferents of flexor muscles
- Extensor half-center: receive inputs from Ia afferents of extensor muscles [23]

    - Other Interneurons
- Neurons with inputs from low-threshold cutaneous afferents (without convergence of high-threshold inputs):
    - Primarily belong to R-cells (extensor half-center)
    - Rarely associated with the flexor half-center
- Typical Ia interneurons (with broad convergence of high-threshold cutaneous and muscle afferents):
    - Mostly belong to the flexor half-center
- Tonically active and indifferent interneurons:
    - Do not exhibit specificity in the organization of ipsilateral afferent inputs
    - May receive signals from various afferent sources

These findings highlight the structured yet flexible organization of the spinal locomotor network, where distinct interneuron populations integrate specific afferent inputs to coordinate locomotor output. The differential recruitment of interneurons based on their afferent connectivity further supports the distributed and hierarchical nature of the central pattern generator (CPG) for locomotion.

3. Contralateral Influences

Characteristic response patterns to contralateral stimulation:

- Most C-interneurons: short-latency inhibition
- Most R-interneurons: short-latency excitation

At the same time, both groups contain units with the opposite type of response

4. Data from Studies on Decorticated Rabbits [24]

Research on spontaneous fictive locomotion in immobilized decorticated rabbits revealed a proposed dorsoventral organization:

- Dorsal regions of the dorsal horn:
    - Neurons with tonic activation during locomotion
- Intermediate zone:
    - Neurons exhibiting tonic inhibition during locomotion
- Ventral regions:
    - Rhythmically active interneurons

However, it should be noted that such strict stratification has not yet been confirmed in other experimental models.

Summary of Findings

The obtained data emphasize the complex yet orderly organization of interneuron networks in the spinal locomotor generator, where:

- Afferent input specificity correlates with neuronal functional affiliation
- Contralateral influences are organized reciprocally
- Spatial distribution of different interneuron types may exhibit species-specific features

1. Confirmation of the Half-Center Concept

The body of experimental data generally supports the hypothesis of flexor and extensor half-centers while revealing additional aspects of their organization:

- Tonically active interneurons may perform modulatory functions:
    - *Tonic excitatory interneurons* – enhance half-center activity
    - *Tonic inhibitory interneurons* – suppress activity, and their inhibition leads to disinhibition of the generator
- Indifferent neurons likely provide:
    - Transmission of afferent information
    - Communication with motoneurons and supraspinal structures

These findings highlight the dynamic and hierarchical nature of spinal locomotor circuits, where both intrinsic rhythm-generating mechanisms and afferent/descending modulation shape locomotor output. The presence of species-specific adaptations further suggests evolutionary flexibility in the organization of central pattern generators (CPGs).

2. Heterogeneity of Temporal Characteristics

Differences in the temporal parameters of interneuron activation may be explained by:

- Variable neuronal excitability
- Specific adaptation mechanisms
- Diverse ratios of excitatory and inhibitory inputs
- Presence of mixed (CR) interneurons capable of modulating motoneuron activation timing

3. Mechanisms of Half-Center Switching

Modern data refine Brown's original hypothesis:

A. Critique of the Passive Fatigue Concept

- Activity switching is likely an active process

- The primary mechanism may involve presynaptic inhibition:
    - Depolarization buildup in synaptic terminals
    - Attainment of a critical inhibition threshold
    - Cessation of excitation in the active half-center
    - Disinhibition of the antagonistic half-center

B. Experimental Evidence [25]

- Identification of axo-axonic synapses not only on primary afferents
- Observation of rhythmic terminal depolarization:
    - In primary afferents during fictive locomotion
    - In spinal interneurons (by analogy)

4. Future Research Directions

Key areas requiring clarification:

- Precise mechanisms of tonic interneuron integration
- Role of presynaptic inhibition in activity switching
- Spatial organization of interneuron subtypes
- Species-specific features of generator networks

Conclusion:

Current evidence positions the spinal locomotor generator as a self-regulating system where:

- Basic rhythm emerges from half-center interactions
- Fine-tuning is mediated by diverse interneuron classes with distinct activation patterns and functional properties

- This framework underscores the interplay between intrinsic rhythmogenesis and adaptive modulation, highlighting the need for further interdisciplinary investigation.

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12. Confirms Brown's half-center model as the foundational CPG framework.
13. Provides experimental data on fictive locomotion, highlighting CPG robustness.
14. Explains afferent/supraspinal interactions in different preparations.
15. DOPA's role in enhancing recurrent inhibition (spinal preparations).
16. Phase-specific Renshaw cell bursts during locomotion (mesencephalic cats).
17. Open questions about γ-motoneuron inhibition and Ia interneurons.
18. Direct electrophysiological evidence for Ia interneuron-mediated IPSPs in motoneurons.
19. Renshaw cells as phase switchers, with experimental manipulation (optogenetics).
20. Updated interneuron taxonomy (C/R/CR/Ta neurons) and CPG architecture.
21. Spatial mapping of locomotor-active interneurons (validating Jankowska's earlier findings)
22. Afferent-specific wiring of Ia interneurons in half-centers
23. Contralateral coordination and species differences (rabbits vs. cats)
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