REVIEW

Neurophysiology of Gait: From the Spinal Cord to the Frontal Lobe

Kaoru Takakusaki, MD, PhD*

The Research Center for Brain Function and Medical Engineering, School of Medicine, Asahikawa Medical University, Asahikawa, Japan; and Department of Precision Engineering, School of Engineering, The University of Tokyo, Tokyo, Japan

ABSTRACT: Locomotion is a purposeful, goal-directed behavior initiated by signals arising from either volitional processing in the cerebral cortex or emotional processing in the limbic system. Regardless of whether the locomotion initiation is volitional or emotional, locomotion is accompanied by automatic controlled movement processes, such as the adjustment of postural muscle tone and rhythmic limb movements. Sensori-motor integration in the brainstem and the spinal cord plays crucial roles in this process. The basic locomotor motor pattern is generated by spinal interneuronal networks, termed central pattern generators (CPGs). Responding to signals in proprioceptive and skin afferents, the spinal interneuronal networks modify the locomotor pattern in cooperation with descending signals from the brainstem structures and the cerebral cortex. Information processing between the basal ganglia, the cerebellum, and the brainstem may enable automatic regulation of muscle tone and rhythmic limb movements in the absence of conscious awareness. However, when a locomoting subject encounters obstacles, the subject has to intentionally adjust bodily alignment to guide limb movements. Such an intentional gait modification requires motor programming in the premotor cortices. The motor programs utilize one's bodily information, such as the body schema, which is preserved and updated in the temporoparietal cortex. The motor programs are transmitted to the brainstem by the corticoreticulospinal system, so that one's posture is anticipatorily controlled. These processes enable the corticospinal system to generate limb trajectory and achieve accurate foot placement. Loops from the motor cortical areas to the basal ganglia and the cerebellum can serve this purpose. © 2013 International Parkinson and Movement Disorder Society

Key Words: central pattern generator; postural muscle tone; corticoreticulospinal system; motor programming; body schema

Gait control requires the activation of the entire nervous system and musculoskeletal system. Because voluntary movements always accompany appropriate postural control, postural control is accomplished through plans and programs that assemble task-related automatic adjustment of movements and posture.[1,2] Therefore, the programs of voluntary movements include those involved in both precise movements of particular body parts and postural adjustments that anticipate the purposeful action. In addition to the execution of movements, the predictive operations of postural programs utilize the cerebral cortex, basal ganglia, cerebellum, and brainstem, whose influences are brought to bear through the descending systems acting on the spinal cord.[1–3]

Similar patterns of neural activity drive locomotion in humans and quadruped animals, which suggests a conserved mechanism during vertebrate evolution.[4] In this review, I first summarize the current understanding of the brainstem-spinal cord mechanisms of generating basic locomotor pattern and controlling postural muscle tone established through animal experimentation, as well as clinical studies. Next, I hypothesize as to the mechanisms of locomotor programming at the level of cerebral cortex in conjunction with the basal ganglia and the cerebellum. An emphasis is placed on the importance of the corticoreticulospinal system in the execution of "anticipatory postural adjustment,"

*Correspondence to: Kaoru Takakusaki, MD, PhD, The Research Center for Brain Function and Medical Engineering, School of Medicine, Asahikawa Medical University, Midorigaoka-Higashi 2-1, 1-1, Asahikawa 078–8511, Japan; kusaki@asahikawa-med.ac.jp

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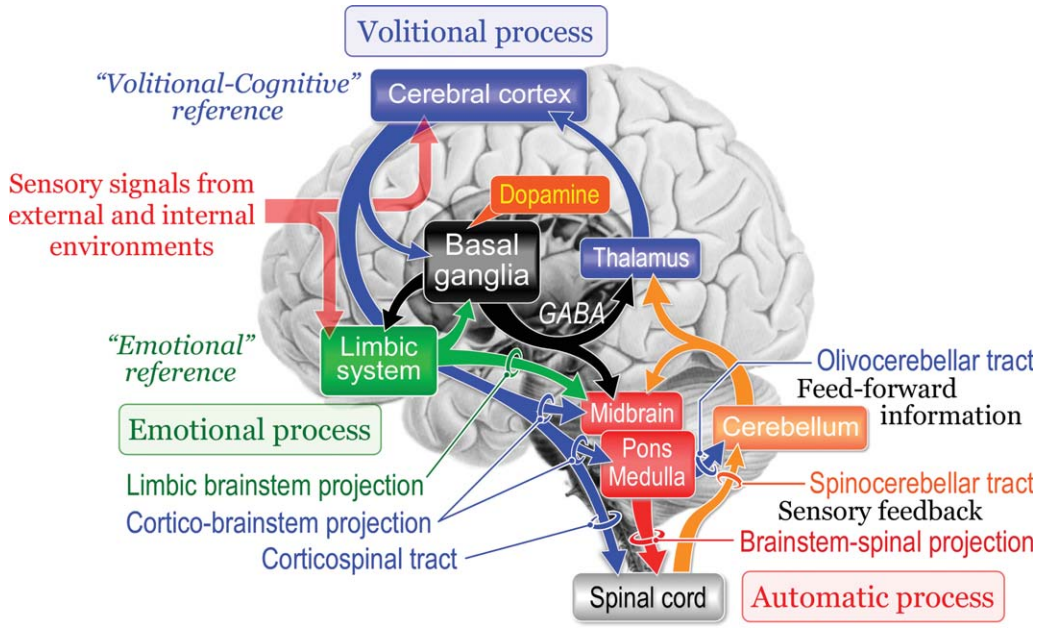

FIG. 1. Fundamental signal flows involved in gait control. (**A**) Schematic illustrations of basic signal flows involved in gait control. Sensory signals acting on the cerebral cortex and limbic system generate "volitional and cognitive reference" and "emotional reference," respectively. The volitional process requires cortical information processing. Projection from the limbic system to the brainstem is responsible for emotional processes. The brainstem (mid-brain, pons, and medulla) and spinal cord are involved in automatic processes. The basal ganglia and the cerebellum control volitional and automatic processes by thalamocortical projections and by direct projections to the brainstem, respectively. See text for further explanation.

which is preparatory postural control that precedes volitional expression of the purposeful action.

Basic Framework of Locomotor Control

Basic signal flows involved in gait control are illustrated schematically in Figure 1.[5] Sensory signals, which are derived from both external stimuli and internal visceral information, have dual functions. One is cognitive processing that is utilized for working memory to guide future behavior and this may affect emotional and arousal states. Accordingly, animals initiate movements depending on either a "volitional or cognitive reference" or an "emotional reference."[6,7] Regardless of whether the locomotion initiation is volitional or emotional, it is accompanied by automatic processes, such as the generation of rhythmic limb movements and the regulation of postural muscle tone.

Goal-directed behaviors may therefore require "volitional," "emotional," and "automatic" processes. The volitional process is derived from intentionally elicited motor commands arising from the cerebral cortex. This process requires activation of various cortical areas and is executed by the corticobrainstem and -spinal projections. The emotional process is elicited by projections from the limbic hypothalamus to the brainstem, resulting in emotional motor behaviors such as fight-or-flight reactions.[7,8] The subject is largely unaware of the automatic process, which is evoked by sequential activations of neurons in the brainstem and spinal cord.

The cerebellum regulates volitional and automatic processes by acting on the cerebral cortex and brainstem, respectively. Real-time sensory feedback by the spinocerebellar tract and feed-forward information from the cerebral cortex by the olivocerebellar tract may play an important role in these operations. The basal ganglia receive inputs from the cerebral cortex and controls volitional, automatic, and emotional processes though gamma-aminobutyric acid (GABA)ergic projections to the cerebral cortex, brainstem, and limbic system, respectively.[5,6,9] GABAergic output is controlled by the midbrain dopaminergic projection.[5,6]

Spinal Locomotor Network Generates Basic Locomotor Pattern

Spinal Interneuronal Network Determines Locomotor Rhythm and Pattern

Isolated spinal cord preparations generate rhythmic burst of reciprocal activity in flexor and extensor muscles, even the absence of sensory input.[9,10] The reciprocal activities are controlled by two systems of spinal interneurons, or "half-centers," which mutually inhibit each other.[9–11] Figure 2 shows the current understanding of the spinal locomotor networks.[9–15] A particular group of spinal interneuronal networks that generates rhythmic activity in the absence of

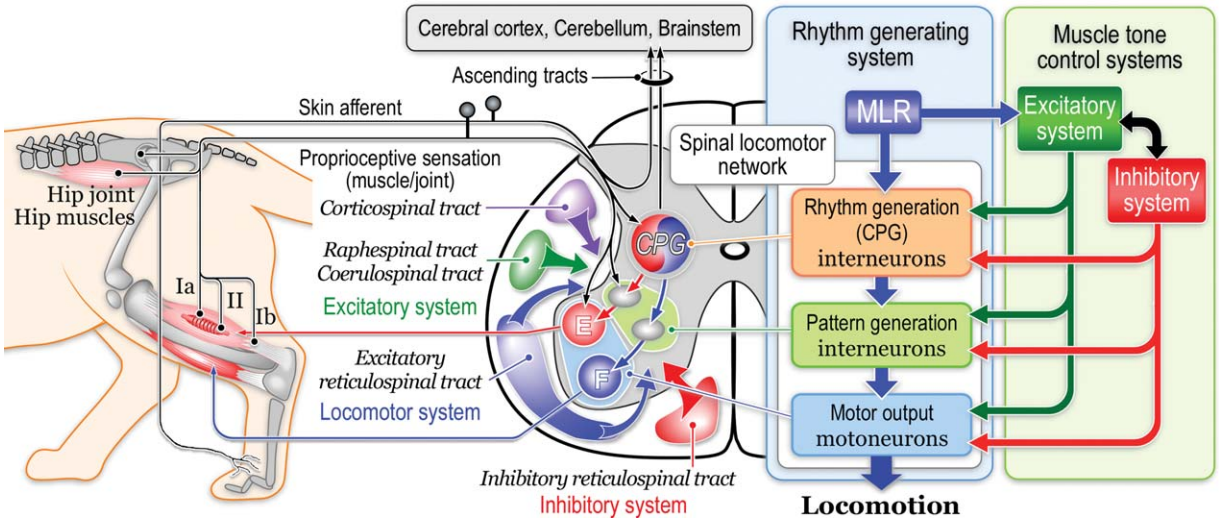

FIG. 2. Spinal mechanisms of locomotor control in animals. Locomotor rhythm and pattern are generated by spinal interneuronal circuits. Activity of spinal neurons is modified by the corticospinal tract and descending tracts from the brainstem. See text for detailed explanations. E; extensor motoneurons; F; flexor motoneurons; Ia, group Ia afferents; Ib, group Ib afferents; II, group II muscle afferents.

rhythmic inputs from sensory afferents is termed central pattern generators (CPGs).[6,7] The basic rhythm is produced by flexor and extensor half-centers. The rhythm interneuronal activity is sent to the second-order interneurons in the intermediate region (lamina IV-VII of Rexed), which shape "locomotor patterns" of each limb's movements.[13–15] The signals are then transmitted to the target motoneurons innervating ipsilateral limb muscles through their excitatory and inhibitory actions.[11] Reciprocal Ia interneurons, classical Ib interneurons, and Renshaw cells are likely included in this group.[13] On the other hand, lamina VIII interneurons projecting to the contralateral side contribute to the left-right alternations of limb movements.[16] The rhythm and pattern are transmitted back to the supraspinal structures by the spinothalamic, -reticular, and -cerebellar tracts, so that the supraspinal structures monitor all events in the spinal cord.[13]

Signals in Sensory Afferents Alter the Organization of the Spinal Locomotor Network

Activity of the spinal locomotor networks is modulated by sensory afferents in a phase-dependent manner.[11,15,17,18] For example, proprioceptors in muscles at the hip joint are primarily responsible for regulating the stance phase. Preventing hip extension suppresses stepping, whereas rhythmically moving the hip can entrain the locomotor rhythm.[17] Afferents from proprioceptors in extensor muscles regulate transition from the stance to swing phase. Signals in Ib afferents from the tendon organ in ankle extensor muscles inhibit homonymous motoneurons in rest, whereas they excite extensor motoneurons during the stance phase.[11,17] The functional consequence of this "reflex reversal" is that the swing phase is not initiated until the extensor muscles are unloaded, and the forces exerted by these muscles are low. The continuous regulation of extensor muscle tone by proprioceptive feedback presumably allows automatic adjustment of force and length in extensor muscles in response to the changes in loading of the leg.

Skin afferents have a powerful influence on the CPG.[11,13,17] Skin receptors are important to detect obstacles and adjust stepping to avoid them, such as the "stumble-corrective reaction."[19] Because this reaction is readily observed in spinal preparation, it must be produced, to a large extent, by spinal circuits. Importantly, the corrective flexion movements are produced only if the paw is stimulated during the swing phase. An identical stimulus applied during the stance phase elicits the opposite response, an excitation of extensor muscles that reinforces the ongoing extensor activity. This is another example of reflex reversal.

The Brainstem Has Core Structures Involved in Postural Control and Locomotion

Locomotor Regions

Figure 3A proposes our current perception of the brainstem mechanisms of locomotion.[5,6,9,20–22] At least three locomotor regions are identified in animals. They are the mid-brain or mesencephalic locomotor region (MLR),[7,9,12] the subthalamic locomotor region (SLR),[7,9,12] and the cerebellar locomotor region (CLR).[23] The MLR is located mostly in the cuneiform nucleus, which is in the vicinity of the pedunculopontine tegmental nucleus (PPN). The lateral part of the mesopontine tegmentum, including these nuclei, receives inputs from the premotor cortices.[24] This area also receives massive inputs from the limbic and

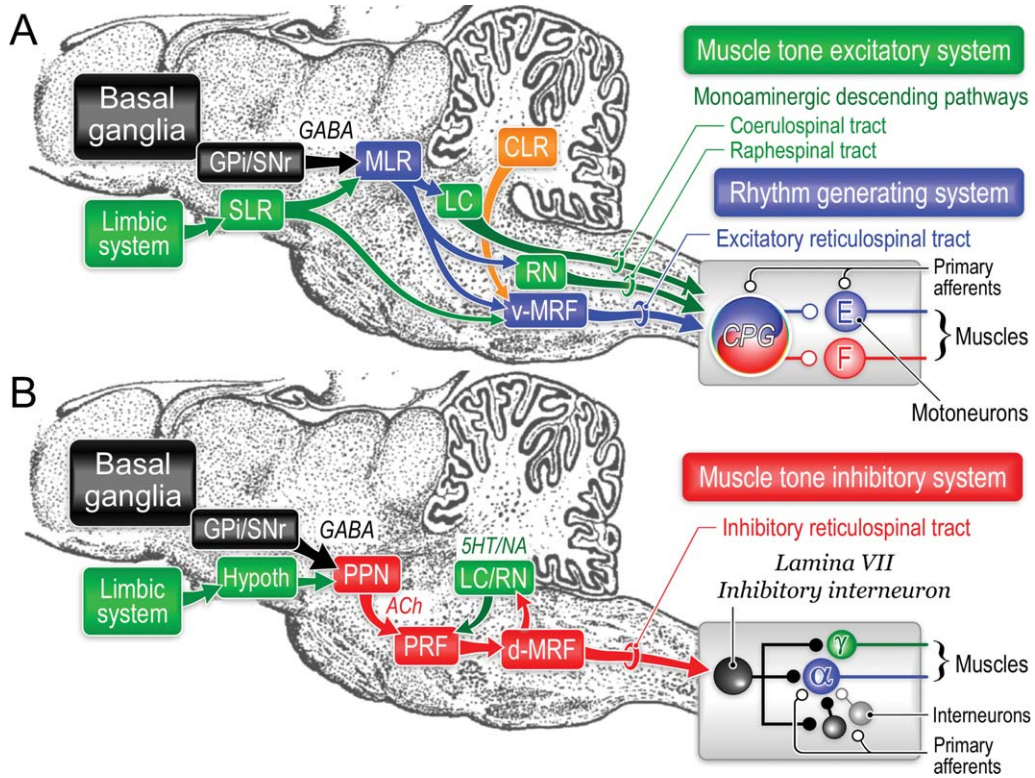

FIG. 3. Brainstem mechanisms of controlling postural muscle tone and locomotion in cats. (**A**) Signals from the MLR activate muscle-tone excitatory and rhythm-generating systems. The rhythm-generating system is from the excitatory reticulospinal tract arising from the ventromedial MRF (v-MRF) and CPG in the spinal cord. The excitatory reticulospinal tract also operates as the muscle-tone excitatory system as well as the coerulospinal tract from the locus coeruleus (LC) and raphespinal tract from the raphe nuclei (RN). Signals from the SLR and those from the CLR activate the rhythm-generating system to evoke locomotion. (**B**) Cholinergic neurons in the PPN activate the muscle-tone inhibitory system, which is composed from the pontine reticular formation (PRF) neurons, inhibitory reticulospinal neurons descending from the dorsomedial MRF (d-MRF), and lamina VII inhibitory interneurons in the spinal cord. Signals from the limbic system act on the muscle-tone inhibitory system through the PPN. GABAergic basal ganglia output from the internal segment of the globus pallidus (GPi) and the SNr to the MLR/PPN controls locomotion and muscle tone. See text for further explanations. 5-HT, serotonin; α, alpha-motoneurons, ACh, acetylcholine; E, extensor motoneurons; F, flexor motoneurons; γ, gamma–motoneurons; Hypoth, hypothalamus; NA, noradrenaline.

hypothalamic areas, including the SLR, by the medial forebrain bundle.[8,9]

Functional imaging studies during mental imagery clearly visualized subcortical structures for postural and locomotor control in humans. These studies show that the most important regions are the mesencephalic, subthalamic, and cerebellar locomotor regions.[25,26] Neurons in these regions, which enable one to initiate or modulate CPG in the cat, may also exist in humans. A clinical study reported a patient with a lesion in the area corresponding to the MLR/PPN, who could not stand or walk.[27] Moreover, the DBS applied to the MLR/PPN with low frequency in Parkinson's disease (PD) patients restored gait capability.[28] However, the clinical benefit of MLR/PPN-DBS remains controversial because of insufficient clinical data at this stage.

Signals from the MLR activate the rhythm-generating system and monoaminergic descending pathways, such as the coerulospinal tract arising from the locus coeruleus and the raphespinal tract from the raphe nuclei.[6,20,29] The rhythm-generating system is comprised of a group of reticulospinal neurons in the ventromedial medullary reticular formation (MRF). This system activates the first- and second-order interneurons sequentially in the spinal locomotor networks (Fig. 2).[11,29] Because the SLR is a part of the lateral hypothalamus, it may contribute to emotional motor behaviors. Signals from the SLR activate the rhythm-generating system either directly or indirectly through the MLR.[8,9,11] The CLR is located in the mid-part of the cerebellar white matter (the hook bundle of Russell).[23] This bundle contains massive crossing fibers from the fastigial nuclei. The output of the CLR possibly activates the rhythm-generating system by projections to the MRF.

Control of Muscle Tone and Locomotion by Descending Pathways From the Brainstem

Several regions in the brainstem are involved in muscle tone regulation. One is an inhibitory region in the PPN.[20,29–31] Cholinergic PPN neurons are considered to excite sequentially pontine reticular formation neurons,[32,33] reticulospinal neurons in the dorsomedial MRF, which correspond to the nucleus reticularis

gigantocellularis,[34] and inhibitory interneurons in the lamina VII in the spinal cord (Fig. 3B).[35] This system inhibits alpha- and gamma-motoneurons innervating extensor and flexor muscles in parallel to interneurons mediating various reflex pathways.[21,22] Therefore, the inhibitory system regulates not only the level of postural muscle tone, but also rhythm and pattern of locomotion (Fig. 2). This inhibitory system may also induce muscular atonia during rapid eye movement sleep.[33–36]

Monoaminergic descending pathways, such as the coerulo- and raphespinal tracts belong to the muscle-tone excitatory system. Because monoaminergic fibers widely arborize in the gray matter,[37] the background excitability of spinal neurons is increased by these tracts so that the spinal locomotor networks sensitively respond to the supraspinal signals and sensory afferents. Emphasis has been placed on the importance of the serotonergic pathway in relation to rhythm generation and the coordination of limb movements during locomotion.[38] In paraplegic rats, grafting of fetal brainstem serotonin neurons in the sublesional spinal cord restored coordinated hindlimb locomotion.[40] Therefore, the intraspinal serotonergic innervation after spinal cord injury is necessary for reorganization of spinal locomotor networks and functional recovery of CPGs.[39]

The excitatory reticulospinal tract from the ventromedial MRF not only activates the spinal rhythm-generating system, but also increases postural muscle tone (Fig. 3B). Level of postural muscle tone is regulated by a counterbalance between the inhibitory and facilitatory systems. There are serotonergic projections to the PPN[41] and the medial pontine reticular formation.[42] The former likely inhibits mesopontine cholinergic neurons,[43] and the latter reduces the activity of the inhibitory system.[34,44] In contrast, the inhibitory system suppresses activity of the coerulospinal tract.[45]

The role of the reticulo- and the vestibulospinal tract neurons has been examined during cat locomotion on an inclined surface. Specifically, the vestibulospinal tract primarily controls the overall level of postural muscle tone, whereas the reticulospinal tract has an additional role in determining the relative level of different muscles, particularly when the pattern is asymmetric.[46] On the other hand, the rubrospinal tract neurons discharge mainly at the end of the stance and during the swing phase of the ipsilateral hindlimb.[47] However, the firing rate increases during voluntary gait modifications in a similar manner to neurons in the motor cortex.[48] Therefore, the rubrospinal tract may regulate flexor muscle activity during locomotion, in particular, limb flexion on the occasion of stepping over the obstacles.

Basal Ganglia Output to the MLR/PPN Modulates Locomotion and Muscle Tone

Experiments in cats showed that the MLR/PPN received GABAergic projection from the substantia nigra pars reticulata (SNr), a basal-ganglia output nucleus.[30,33,36] An increase in the GABAergic output from the SNr by electrical stimulation with a frequency of 50 to 100 Hz reduced the activity of the MLR rhythm-generating system and the PPN muscle-tone inhibitory system, resulting in suppression of locomotion and an increase in postural muscle tone. However, high-frequency stimulation (150–200 Hz) of the SNr was not effective.[30,33,36] These findings are clinically important because the output of the basal ganglia is considered to be increased in PD.[49] Excessive GABAergic inhibitory effects upon the MLR/PPN may be a pathophysiological basis of gait disturbance and muscle tone rigidity (hypertonus) in this disease.[5,6,29] Moreover, a clinical study showed that DBS applied to the SNr with high frequency (130–190 Hz) improved axial motor symptoms, such as gait failure and postural disturbances, in patients with PD.[50]

Contribution of Cerebral Cortex to the Postural and Locomotor Synergies

Motor Programs in the Frontal Lobe

Figure 4 illustrates suggested signal flows from the cerebral cortex to the spinal cord in relation to postural and locomotor control. Because patients with dysfunction of the frontal lobe, including the premotor area (PM) and the supplementary motor area (SMA), exhibit freezing of gait, these areas play crucial roles for gait initiation.[51–54] Motor programs of voluntary movements include those for postural adjustment.[1] This may enable anticipatory postural control, which may be carried by the activation of SMA.[1,55] The PM, particularly on the right side, is activated during paradoxical gait in PD, indicating that the PM is responsible for motor programming based on visuomotor processing.[56] In recent studies using bipedally walking monkeys, microinjections of muscimol ($GABA_A$-receptor agonist) into the leg region of the primary motor cortex (M1) resulted in local paresis of the contralateral leg.[57] On the other hand, muscimol injections into trunk/leg regions of the bilateral SMA disturbed postural control during walking without motor paralysis.[58] When muscimol was injected into the dorsal PM, the monkey could not start walking after sensory guidance. However, spontaneous walking was not affected. Accordingly, the SMA may contribute to postural control, whereas the dorsal PM may be responsible for sensory-guided gait initiation.

Parietofrontal Connection and the Corticoreticulospinal Pathway Contribute to Anticipatory Postural Control

Although neurons in the M1 project mainly to the spinal cord, neurons in the SMA/PM have dense

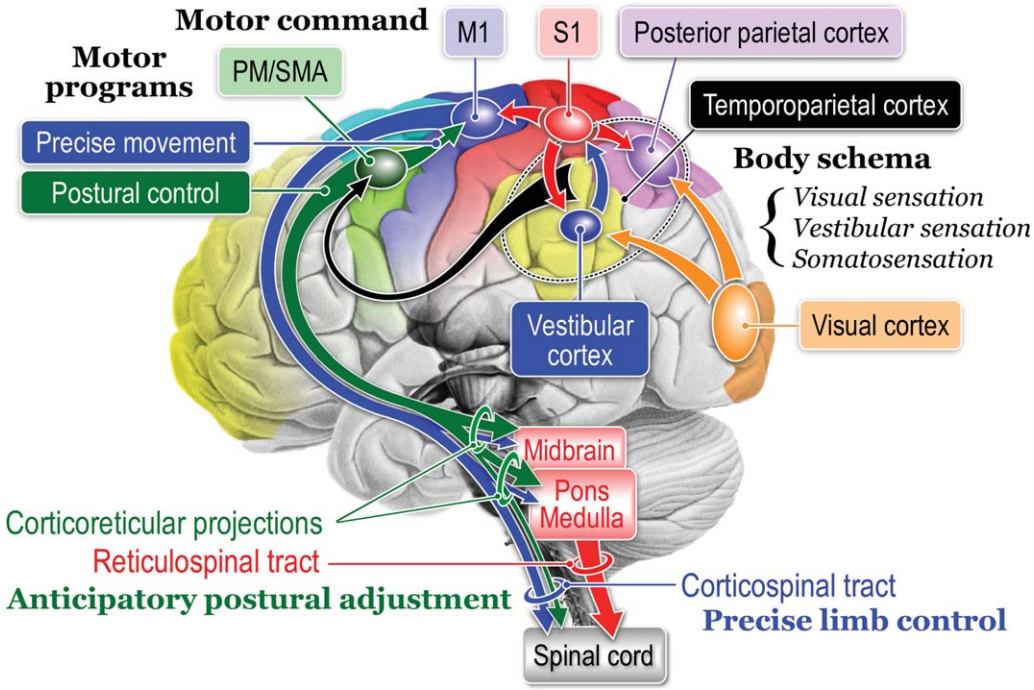

FIG. 4. Cortical mechanisms involved in movement control. Motor programs of precise movement and postural control are generated in the premotor area (PM) and the supplementary motor area (SMA). Descending signals from these areas to the brainstem by the corticoreticular projection may contribute to anticipatory postural adjustment by activating the reticulospinal tract. Motor command for precise limb control during locomotion is carried by the corticospinal tract arising from the primary motor cortex (M1). Somatosensory, vestibular, and visual sensations are integrated at the temporoparietal-posterior parietal cortices, where the body schema is generated and updated. This bodily information is transmitted to the PM/SMA and is utilized to generate motor programs. S1, primary sensory cortex.

projections to the pontomedullary reticular formation in addition to the spinal cord (Fig. 4).[24,59] The reticulospinal tract innervates whole spinal segments,[16] so that it controls postural muscle tone[21] and symmetric postural figures.[60] Therefore, the corticoreticular and the reticulospinal tract may achieve postural preparation or anticipatory postural adjustment that precedes gait initiation. It is particularly important to determine whether these pathways contribute to the anticipatory postural adjustment by using animal experimentation and clinical examination. On the other hand, the PM/SMA may forward programs of precise leg-foot movement to the M1,[61] which, in turn, sends motor command by the corticospinal tract.

When a locomoting subject encounters obstacles, each foot must be placed with a high degree of accuracy. This accuracy requires a precise visuomotor coordination, in which the subject has to modify the limb trajectory in each step.[62] The posterior parietal cortex has an essential role in the above-mentioned process.[63,64] Visual information about the size and location of an obstacle is registered and stored in short-term memory to guide the legs. In quadrupeds, such a working memory is particularly necessary because an obstacle is no longer within the visual field by the time the hindlimbs are stepping over it. Importantly, the short-term memory is always associated with one's bodily information as the "body schema." The body schema is an internal postural model, which is a perception of one's body in space and body parts associated with movement, and is critical for visuomotor processing.[1] The temporoparietal cortex, including the posterior parietal cortex and the vestibular cortex, appears to integrate real-time signals in the visual, proprioceptive, and vestibular sensations so that the body schema can be always updated (Fig. 4).[51,65] Then, this bodily information is utilized to generate motor programs in the PM/SMA. Consequently, cognitive information processing in the temporoparietal cortex is essential for accurate gait control, particularly when the subject encounters an unfamiliar environment. Therefore, the deficiency in the information processing from the temporoparietal cortex to the frontal cortex may cause errors in anticipatory postural adjustment and gait difficulties, such as the "freezing of gait." It follows that deficits in cognitive function in elder persons and in patients with Alzheimer's disease are at higher risk of falling, particularly when more-cognitive tasks are required.[66,67]

Difference in the Operation of Locomotor Systems Between Quadruped and Biped

The operation of the locomotor system in biped animals is unclear. Nakajima et al. recorded single-unit activities from the trunk/leg regions of M1 during

quadru- and bipedal locomotion in unrestrained Japanese monkeys.[68] Although the majority of M1 neurons exhibited discharges in relation to the locomotor step cycles, firing rates of each neuron increased at the transition from quadru- to bipedal locomotion. The higher activity in the M1 neurons was associated with significant increase in the contractions of all the trunk and leg muscles. The increase in M1 activity during bipedal locomotion may reflect higher cortical processing than quadrupedal locomotion.

Changes in proprioceptive, visual, and vestibular information in the temporoparietal cortex may alter the body schema, which, in turn, develops motor programming in the SMA/PM. This may enable animals to achieve more-exquisite feed-forward control of postural and locomotor synergies (eg, anticipatory postural adjustment) during bipedal locomotion. Enhancement of muscle contractions in trunk and leg muscles during bipedal locomotion reflects the higher excitability of the spinal locomotor networks, which is caused by an increase in the signals from the supraspinal descending pathways and proprioceptive sensations. Changes from quadru- to bipedal locomotion may require functional reorganization of the supraspinal and spinal motor systems. Because subcortical mechanisms are common in humans (bipeds)[25,26] and cats (quadrupeds),[7,9,12,23] the difference in cortical processing during locomotion between bipeds and quadrupeds may be a key mechanism of vertebrate evolution.[4]

Role of the Basal Ganglia and the Cerebellum

Adaptive gait control requires constant recalibration of walking pattern to navigate different terrains and environments. For example, motor cortical neurons do not exhibit altered discharge during steady-state locomotion, but altered discharge occurs when the experimental animal has to overcome obstacles.[69] Loops from the motor cortical areas to the basal ganglia and the cerebellum may contribute to this purpose (ie, contribute to accurate and adaptive movement control that requires volition, cognition, attention, and prediction).[3,70] In contrast, cortical processing seems unnecessary during the automatic execution of locomotion. Rather, high-level processing may occur in the systems between the basal ganglia, cerebellum, and brainstem in the absence of conscious awareness.[5]

Patients with cerebellar damage can make reactive changes normally during walking, but are impaired when attempting to learn predictive changes.[70] However, patients with cerebral damage from stroke have a normal capacity to make both reactive and predictive locomotor adaptations during walking.[71] Therefore, predictive control in human locomotion appears to depend specifically on cerebellar mechanisms that may modulate the output of spinal locomotor networks that form basic rhythmic limb movements during walking.[72]

The brainstem receives excitatory inputs from the cerebral cortex, limbic system, and cerebellum as well as inhibitory inputs from the basal ganglia (Fig. 1). The MLR/PPN and the pontomedullary reticular formation receive inputs more preferentially from the SMA and PM, rather than M1.[24,60] It follows that the signals from the basal ganglia and the cerebellum control the excitability of neurons in the cerebral cortex and the brainstem by ascending and descending projections, respectively.[73] The former contributes to planning, programming, and gait initiation. The latter may modulate locomotor rhythm and postural muscle tone during locomotion. ■

References

1. Massion J. Movement, posture and equilibrium: interaction and coordination. Prog Neurobiol 1992;38:35–36.
2. Brooks VB, III. Posture and locomotion. In: The Neural Basis of Motor Control. New York: Oxford University Press; 1986:140–150.
3. Middleton FA, Strick PL. Basal ganglia and cerebellar loops: motor and cognitive circuits. Brain Res Rev 2000;31:236–250.
4. Grillner S. Human locomotor circuits conform. Science 2011;344: 912–913.
5. Takakusaki K, Tomita N, Yano M. Substrates for normal gait and pathophysiology of gait disturbances with respect to the basal ganglia dysfunction. J Neurol 2008;255(Suppl 4):19–29.
6. Takakusaki K. Forebrain control of locomotor behaviors. Brain Res Rev 2008;57:192–198.
7. Grillner S, Georgopoulos AP, Jordan LM. Selection and initiation of motor behavior. In: Stein PSG, Grillner S, Selverston AI, Stuart DG, editors. Neurons, Networks, and Motor Behavior. Cambridge, MA: MIT Press; 2002:3–19.
8. Sinnamon HM. Preoptic and hypothalamic neurons and initiation of locomotion in the anesthetized rat. Prog Neurobiol 1993;41: 323–344.
9. Grillner S. Control of locomotion in bipeds, tetrapods, and fish. In: Brooks VB, editor. The Nervous System II. Bethesda, MD: Am Physiol Soc Press; 1981:1179–1236.
10. Boothe DL, Cohen AH, Troyer TW. Phase locking asymmetries at flexor-extensor transitions during fictive locomotion. PLoS One 2013:8:e64421.
11. Rossignol S, Dubuc R, Gossard J-P. Dynamic sensorimotor interactions in locomotion. Physiol Rev 2006;86:89–154.
12. Mori S. Integration of posture and locomotion in acute decerebrate cats and in awake, freely moving cats. Prog Neurobiol 1987;28: 161–196.
13. Rossignol S. Neural control of stereotypic limb movements. In: Rowell LB, Shepherd JT, editors. Handbook of Physiology, sec. 12. New York: Oxford University Press; 1996:173–216.
14. Takakusaki K, Kohyama J, Matsuyama K. Medullary reticulospinal tract mediating a generalized motor inhibition in cats: III. Functional organization of spinal interneurons in the lower lumbar segments. Neuroscience 2003;121:731–746.
15. McCrea DA, Rybak IA. Organization of mammalian locomotor rhythm and pattern generation. Brain Res Rev 2008;57:134–146.
16. Matsuyama K, Takakusaki K. Organizing principles of axonal projections of the long descending reticulospinal pathway and its target spinal lamina VIII commissural neurons: with special reference to the locomotor function. In: Westland TB, Calton RN, editors. Handbook on White Matter: Structure, Function and Changes, chapter XVIII. New York: Nova Science; 2009:335–356.
17. Pearson KG. Generating the walking gait: role of sensory feedback. Prog Brain Res 2003;143:123–129.

18. Frigon A, Sirois J, Gossard JP. Effects of ankle and hip muscle afferent inputs on rhythm generation during fictive locomotion. J Neurophysiol 2010;103:1591–1605.

19. Forssberg H. Stumbling corrective reaction: a phase dependent compensatory reaction during locomotion. J Neurophysiol 1979; 42:936–953.

20. Takakusaki K, Saitoh K, Nonaka S, et al. Neurobiological basis of state-dependent control of motor behavior. Sleep Biol Rhyth 2006; 4:87–104.

21. Takakusaki K, Kohyama J, Matsuyama K, et al. Medullary reticulospinal tract mediating the generalized motor inhibition in cats: parallel inhibitory mechanisms acting on motoneurons and on interneuronal transmission in reflex pathways. Neuroscience 2001; 103:511–527.

22. Takakusaki K, Kohyama J, Matsuyama K. Medullary reticulospinal tract mediating a generalized motor inhibition in cats: III. Functional organization of spinal interneurons in the lower lumbar segments. Neuroscience 2003;121:731–746.

23. Mori S, Matsui T, Kuze B, et al. Stimulation of a restricted region in the midline cerebellar white matter evokes coordinated quadrupedal locomotion in the decerebrate cat. J Neurophysiol 1999;82: 290–300.

24. Matsuyama K, Drew T. Organization of the projections from the pericruciate cortex to the pontomedullary brainstem of the cat: a study using the anterograde tracer Phaseolus vulgaris-leucoagglutinin. J Comp Neurol 1997;389:617–641.

25. Jahn K, Deutschländer A, Stephan T, et al. Supraspinal locomotor control in quadrupeds and humans. Prog Brain Res 2008;171:353–362.

26. Jahn K, Deutschländer A, Stephan T, et al. Imaging human supraspinal locomotor centers in brainstem and cerebellum. Neuroimage 2008;39:786–792.

27. Masdeu JC, Alampur U, Cavaliere R, et al. Astasia and gait failure with damage of the pontomesencephalic locomotor region. Ann Neurol 1994;35:619–621.

28. Stefani A, Lozano AM, Peppe A, et al. Bilateral deep brain stimulation of the pedunculopontine and subthalamic nuclei in severe Parkinson's disease. Brain 2007;13:1596–1607.

29. Takakusaki K, Saitoh K, Harada H, et al. Role of basal ganglia—brainstem pathways in the control of motor behaviors. Neurosci Res 2004;50:137–151.

30. Takakusaki K, Habaguchi T, Ohtinata-Sugimoto J, Saitoh K, Sakamoto T. Basal ganglia efferents to the brainstem centers controlling postural muscle tone and locomotion: a new concept for understanding motor disorders in basal ganglia dysfunction. Neuroscience 2003;119:293–308.

31. Takakusaki K, Habaguchi T, Saitoh K, Kohyama J. Changes in the excitability of hindlimb motoneurons during muscular atonia induced by stimulating the pedunculopontine tegmental nucleus in cats. Neuroscience 2004;124:467–480.

32. Lai YY, Clements JR, Siegel JM. Glutamatergic and cholinergic projections to the pontine inhibitory area identified with horseradish peroxidase retrograde transport and immunohistochemistry. J Comp Neurol 1993;336:321–330.

33. Takakusaki K, Obara K, Nozu T, et al. Modulatory effects of the GABAergic basal ganglia neurons on the PPN and the muscle tone inhibitory system in cats. Arch Ital Biol 2011;149:385–405.

34. Takakusaki K, Shimoda N, Matsuyama K, et al. Discharge properties of medullary reticulospinal neurons during postural changes induced by intrapontine injections of carbachol, atropine and serotonin, and their functional linkages to hindlimb motoneurons in cats. Exp Brain Res 1994;99:361–374.

35. Takakusaki K, Saitoh K. A new category of spinal interneurons that mediate muscular atonia in cats. Soc Neurosci Abstr 2005; 863:17/Z20.

36. Takakusaki K, Saitoh K, Harada H, et al. Evidence for a role of basal ganglia in the regulation of rapid eye movement sleep by electrical and chemical stimulation for the pedunculopontine tegmental nucleus and the substantia nigra pars reticulata in decerebrate cats. Neuroscience 2004;124:207–220.

37. Basubaum AL, Fields HL. Endogenous pain control systems: brainstem spinal pathways and endorphin circuitry. Ann Rev Neurosci 1984;7:309–338.

38. Sławińska U, Majczyński H, Dai Y, et al. The upright posture improves plantar stepping and alters responses to serotonergic drugs in spinal rats. J Physiol 2012;590:1721–1736.

39. Sławińska U, Miazga K, Cabaj AM, et al. Grafting of fetal brainstem 5-HT neurons into the sublesional spinal cord of paraplegic rats restores coordinated hindlimb locomotion. Exp Neurol. 2013; 247:572–581.

40. Cohen AH, Abdelnabi M, Guan L, et al. Changes in distribution of serotonin induced by spinal injury in larval lampreys: evidence from immunohistochemistry and HPLC. J Neurotrauma 2005;22: 172–188.

41. Honda T, Semba K. Serotonergic synaptic input to cholinergic neurons in the rat mesopontine tegmentum. Brain Res 1994;647:299–306.

42. Semba K. Aminergic and cholinergic afferents to REM sleep induction regions of the pontine reticular formation in the rat. J Comp Neurol 1993;330:543–556.

43. Leonald CS, Llinás R. Serotonergic and cholinergic inhibition of mesopontine cholinergic neurons controlling REM sleep: an in vitro electrophysiological study. Neuroscience 1994;59:309–330.

44. Takakusaki K, Kohyama J, Matsuyama K, et al. Synaptic mechanisms acting on lumbar motoneurons during postural augmentation induced by serotonin injection into the rostral pontine reticular formation in decerebrate cats. Exp Brain Res 1993;93: 471–482.

45. Mileykovskiy BY, Kiyashchenko LI, Kodama T, et al. Activation of pontine and medullary motor inhibitory regions reduces discharge in neurons located in the locus coeruleus and the anatomical equivalent of the midbrain locomotor region. J Neurosci 2000; 20:8551–8558.

46. Matsuyama K, Drew T. Vestibulospinal and reticulospinal neuronal activity during locomotion in the intact cat. II. Walking on an inclined plane. J Neurophysiol 2000;84:2257–2276.

47. Arshavsky YI, Orlovsky GN, Perret C. Activity of rubrospinal neurons during locomotion and scratching in the cat. Behav Brain Res 1988;28:193–199.

48. Rho MJ, Lavoie S, Drew T. Effects of red nucleus microstimulation on the locomotor pattern and timing in the intact cat: a comparison with the motor cortex. J Neurophysiol 1999;81:2297–2315.

49. Delong MR. Primate models of movement disorders of basal ganglia origin. Trends Neurosci 1990;13:281–2890.

50. Chastan N, Westby GW, Yelnik J, et al. Effects of nigral stimulation on locomotion and postural stability in patients with Parkinson's disease. Brain 2009;132:172–184.

51. Bartels AL, Leenders KL. Brain imaging in patients with freezing of gait. Mov Disord 2008;23(Suppl):S461–S467.

52. Nutt JG, Marsden CD, Thompson PD. Human walking and higher-level gait disorders, particularly in the elderly. Neurology 1993;43:268–279.

53. Hanakawa T, Katsumi Y, Fukuyama H, et al. Mechanisms underlying gait disturbance in Parkinson's disease: a single photon emission computed tomography study. Brain 1999;122:1271–1282.

54. Nutt JG, Bloem BR, Giladi N, Hallet M, Horak FB, Nieuwboer A. Freezing of gait: moving forward on a mysterious clinical phenomenon. Lancet Neurol 2011;10:734–744.

55. Wiesendanger M, Hummelsheim H, Biancrethi M, et al. Input and output organization of the supplementary motor area. In: Motor Area of the Cerebral Cortex, CIBA Foundation Symposium 132. Chichester, UK: Wiley; 1987:40–62.

56. Hanakawa T, Fukuyama H, Katsumi Y, et al. Enhanced lateral premotor activity during paradoxical gait in Parkinson's disease. Ann Neurol 1999;45:329–336.

57. Nakajima K, Mori F, Tachibana A, et al. Cortical mechanisms for the control of bipedal locomotion in Japanese monkeys: I. Local inactivation of the primary motor cortex (M1). Neurosci Res 2003;46(Suppl 1):S156.

58. Mori F, Nakajima K, Tachibana A, et al. Cortical mechanisms for the control of bipedal locomotion in Japanese monkeys: II. Local inactivation of the supplementary motor area (SMA). Neurosci Res 2003;46(Suppl 1):S157.

59. Keizer K, Kuypers HG. Distribution of corticospinal neurons with collaterals to the lower brain stem reticular formation in monkey (Macaca fascicularis). Exp Brain Res 1989;74:311–318.

60. Drew T, Rossignol S. Functional organization within the medullary reticular formation of the intact unanesthetized cat. II. Electromyographic activity evoked by microstimulation. J Neurophysiol 1990; 64:782–795.

61. Hoshi E, Tanji J. Distinctions between dorsal and ventral premotor areas: anatomical connectivity and functional properties. Curr Opin Neurobiol 2007;17:234–242.

62. Georgopoulos AP, Grillner S. Visuomotor coordination in reaching and locomotion. Science 1989;245:1209–1210.

63. Marigold DS, Drew T. Contribution of cells in the posterior parietal cortex to the planning of visually guided locomotion in the cat: effects of temporary visual interruption. J Neurophysiol 2011;105: 2457–2470.

64. Lajoie K, Andujar JE, Pearson K, Drew T. Neurons in area 5 of the posterior parietal cortex in the cat contribute to interlimb coordination during visually guided locomotion: a role in working memory. J Neurophysiol 2010;103:2234–2254.

65. Brandt T, Dieterich M. The vestibular cortex: its locations, functions, and disorders. Ann N Y Acad Sci 1999;871:293–312.

66. Snijders AH, van de Warrenburg BP, Giladi N, et al. Neurological gait disorders in elderly people: clinical approach and classification. Lancet Neurol 2007;6:63–74.

67. Cohen RG, Nutt JG, Horak FB. Errors in postural preparation lead to increased choice reaction times for step initiation in older adults. J Gerontol A Biol Sci Med Sci. 2011;66:705–713.

68. Nakajima K, Mori F, Murata A. Inase M. Neuronal activity in primary motor cortex during quadrupedal versus bipedal locomotion of an unrestrained Japanese monkey. Soc Neurosci Abstract 2010; 183:2

69. Drew T, Jiang W, Kably B, et al. Role of the motor cortex in the control of visually triggered gait modifications. Can J Physiol Pharmacol 1996;74:426–442.

70. Reisman DS, Block HJ, Bastian AJ. Interlimb coordination during locomotion: what can be adapted and stored? J Neurophysiol 2005;94:2403–2415.

71. Morton SM, Bastian AJ. Cerebellar contributions to locomotor adaptations during splitbelt treadmill walking. J Neurosci 2006;26: 9107–9116.

72. Choi JT, Bastian AJ. Adaptation reveals independent control networks for human walking. Nat Neurosci 2007;20:1055–1062.

73. Hikosaka O, Takikawa Y, Kawgoe R. Role of the basal ganglia in the control of purposive saccadic eye movements. Physiol Rev 2000;80:954–978.