Brain Research Reviews (2008) 57(1):192-198.

Forebrain control of locomotor behaviors

Takakusaki, Kaoru

BRAIN RESEARCH REVIEWS

Mini-Review; Wenner-Gren Foundation (WGF) International Symposium

Forebrain control of locomotor behaviors

Kaoru Takakusaki, M.D., Ph.D.
Department of Physiology, Division of Neural Function, Asahikawa Medical College,
Asahikawa 078-8510, Japan

Address all corresponding to:
Kaoru Takakusaki, M.D., Ph.D.
Associate Professor
Department of Physiology, Division of Neural Function
Asahikawa Medical College,
Midorigaoka-Higashi, 2-1, Asahikawa 078-8510, JAPAN

TEL; +81-166-68-2331
FAX; +81-166-68-2339
E-mail kusaki@asahikawa-med.ac.jp

ABSTRACT

Activation of different areas in the forebrain evokes different types of goal directed adaptive behaviors. An important component of these different patterns of behavior is the locomotion that brings the animal to or away from a particular location. Here I review the role of projections from forebrain structures to the mesopontine tegmentum of the brainstem where neural mechanisms for initiation of locomotion and regulation of postural muscle tone are located that are activated during locomotor behavior. It is interesting is to understand how signals that converge from the forebrain structures to the mesopontine tegmentum control locomotor behavior, because the mesopontine tegmentum receives inhibitory efferents from the basal ganglia and excitatory efferents from the limbic-hypothalamic system and the neocortex. Here I hypothesize that the mesopontine tegmentum has functional gating mechanisms that determine whether the subject will initiate and select volitionally-guided or emotionally-triggered locomotor behaviors, depending on the behavioral context.

CONTENTS

Keywords

- Basal ganglia
- Limbic-hypothalamus system
- GABA
- Orexin
- Locomotor behavior
- Postural muscle tone

1. Introduction: Framework of locomotor behavior.

It is most essential that the cognitive and bodily functions of all animals are adapted to external conditions. An adaptive capability will be achieved mostly through the motor behavior that depends on factors such as the intention of an individual and the emotional state. Sensory signals, derived from both external stimuli and internal visceral information, have dual roles. One role is to generate cognitive cortical processing which is utilized for the working memory and can be used for guide future behavior. The other may be to affect the “emotional states” of the animal.

After ablation of a large part of striatum bilaterally, external stimuli have been reported to make animal follow any object that moves. Denny-Brown (1962) referred to this behavior as a “visually-determined cortical automatism”. On the other hand after removal of the cat cerebral cortex but preserving the bilateral striatum, the animals were hyper-responsible to stimuli, so that considerable variation in emotional reactions occurred (Villabranca and Olmstead, 1982). Removal of both the cerebral cortex and the striatum (the thalami and hypothalamus were preserved) forced the animals to walk incessantly, even though they did not attend to any environmental stimuli (Villabranca and Marcus, 1972). These findings lead us to postulate that the basal ganglia are involved in the visuomotor coordination of cognitive, and the emotional expression of locomotor behavior.

Locomotion has been considered as a type of emotional motor behavior triggered by signals from the limbic-hypothalamic system to the brainstem (Sinnamon, 1993). However, stepping movements with very accurate foot placement resemble the forelimb reaching movements of higher primates (Drew et al., 2004; Georgopoulos and Grillner, 1989). Locomotion therefore also requires visuomotor cognitive processes which are controlled by loops involving the cerebral cortex, basal ganglia and cerebellum (Middleton and Strick, 2000). Whether the locomotion is either volitional or emotional, it

is accompanied by movement processes that are automatically controlled by the brainstem and spinal cord. The automatic processes include activation of sequences of basic motor programs that are designed for the basic motor repertoires such as eye movements, swallowing, locomotion and posture (Hikosaka et al., 2000). The basic neuronal structures for locomotion are located in the mesopontine tegmentum. One structure is the mesencephalic locomotor region (MLR), and the other is the muscle tone inhibitory region in the pedunculopontine nucleus (PPN; Takakusaki, 2003b, 2004a). For a thorough understanding of "locomotor behavior" further elucidation is therefore necessary to explain how efferents from the forebrain modulate the activity of these midbrain motor centers.

Here, I propose mechanisms for understanding the initiation, integration, and selection of locomotor behavior. There are three key points in the mechanisms. The first is that the basic locomotor systems are regulated by a balance between net excitation from the cerebral cortex and the limbic-hypothalamic system, and net inhibition from the basal ganglia. The second, which I particularly focus on here, is the roles of "GABAergic basal ganglia efferents" and "orexinergic hypothalamic efferents" to the mesopontine tegmentum. The third is that the locomotor behavior depends on an excitability preference of the forebrain and hindbrain. The functional implication of this model is also discussed in relation to the pathophysiological mechanisms of motor deficiencies in Parkinson disease and cataplexy in narcolepsy.

2. Basic neuronal mechanisms for controlling locomotion and postural muscle tone.

In decerebrate (Shik et al., 1966; Takakusaki et al., 2003b) and alert (Mori, 1987) cats, locomotion is evoked by either electrical or chemical stimulation of the MLR. The MLR largely corresponds to the cuneiform nucleus (CNF) and a region of the PPN (Fig.1Cb). The non-cholinergic neurons in these areas are possibly involved in the

generation of locomotion (Jordan, 1998; Takakusaki, 2003b). Intracellular recording of extensor (soleus) motoneurons in immobilized preparations has revealed that stimulation of the MLR first depolarized the membrane potential and then generated rhythmic membrane oscillations which were accompanied by burst firing (Fig.1Ba). Therefore, signals from the MLR activate two systems. One system is the “muscle tone excitatory system” arising from the locus coeruleus (LC), raphe nuclei, and excitatory reticulospinal system. The other is the “locomotor rhythm generating system” which is composed of the medullary reticulospinal tract, and central pattern generators (CPGs) in the spinal cord (Fig.1A; Grillner, 1981).

On the other hand, either electrical or chemical stimulation applied to the ventrolateral PPN (Fig.1Cb) was observed to suppress postural muscle tone in decerebrate cats. The PPN-induced muscular atonia is often accompanied by rapid eye movements (REM; Takakusaki et al., 2003b, 2004a). Through postsynaptic inhibition, PPN stimulation hyperpolarized motoneurons innervating extensor and flexor muscles (Fig.1 Bb). A histological assessment revealed that cholinergic neurons are preferentially distributed in the inhibitory region rather than the locomotor region. Ascending neurons in the PPN project to the basal ganglia nuclei, non-specific thalamic nuclei, and superior colliculus, in addition to descending projections to the pontomedullary reticular formation (see Takakusaki et al., 2004b).

The PPN-induced atonia was blocked by an injection of atropine sulfate into the medial pontine reticular formation (PRF) corresponding to the nucleus reticularis pontis oralis (NRPo). We consider that stimulation of the PPN excites cholinoceptive NRPo neurons, which, in turn, activate reticulospinal neurons in the medullary nucleus reticularis gigantocellularis (NRGc) so that extensor and flexor motoneurons are inhibited via spinal inhibitory interneurons (Takakusaki et al., 1994, 2003b). The “muscle tone inhibitory system” provides postsynaptic inhibitory effects upon α- and

γ-motoneurons, in parallel to interneurons intercalated in reflex pathways to motoneurons (Takakusaki et al., 2001, 2003c). This system may also suppress CPGs in the spinal cord, as well as motoneurons, resulting in attenuation of locomotion (Fig. 1A).

A clinical report has noted that a patient with a lesion in the dorsal part of the mesopontine tegmentum could not stand or walk (astasia) without any motor paralyses (Masdue et al., 1994). In addition, it has been observed that a patient with a lesion in the dorsolateral mesopontine tegmentum did not lose muscle tone during REM sleep (Culebras et al., 1989). These clinical cases suggest that both an MLR, and a muscle tone, inhibitory region are present in humans.

3. Control of locomotor behavior by basal ganglia brainstem (BG-BS) projections.

3.1. Modulation of locomotion and muscle tone.

In rats (Spann and Grofova, 1991; Saitoh et al., 2003) and cats (Moriizumi et al., 1988), GABAergic neurons arising from the substantia nigra pars reticulata (SNr) and the entopeduncular nucleus, which corresponds to the internal segment of the globus pallidus in primates, project to the mesopontine tegmentum. These projections include those to the MLR and the PPN. Because the neuronal activity of the MLR and the PPN is under a tonic GABAergic influence from the SNr, the basal ganglia could be responsible for controlling postural muscle tone which is associated with locomotor behavior.

Takakusaki et al. (2003b) have revealed that GABAergic SNr neurons modulated locomotion and postural muscle tone. Although electrical stimuli applied to the SNr (20 - 50 μA, 100 Hz) alone did not alter muscle tone, it disturbed the MLR-induced locomotion: the onset of locomotion was delayed, and step cycles were increased as the stimulus intensity was increased. The locomotion was finally abolished by a higher current of the SNr stimuli (50 μA). The optimal sites for disturbing the locomotion were

located in the medial and middle parts of the SNr. On the other hand, stimulation of the middle or lateral SNr (20 - 40 μA, 100 Hz) attenuated PPN-induced muscle tone suppression (Fig.1Ca). By increasing the stimulus intensity (50 μA) the PPN-effect was diminished. In addition, these SNr effects were blocked by micro-injections of $GABA_A$-receptor antagonists (bicuculline or picrotoxin; 2.0 - 5.0 μM, 0.1 - 0.25 μl) into the MLR or the PPN. Moreover, inactivation of the medial and lateral SNr by microinjections of muscimol (a $GABA_A$-receptor agonist) induced locomotion and muscular atonia, respectively (Takakusaki et al., 2004a). All of these findings corroborate that the SNr GABAergic neurons projecting to the MLR/PPN control locomotion and muscle tone, and there is a functional organization in the nigrotegmental projections: medial and lateral SNr neurons may modulate locomotion and muscle tone respectively (Takakusaki et al., 2003b). Furthermore, with stimulation of the PRF, MRF, and the LC, the amplitude of the EPSPs were increased instead of a reduction of the IPSP components during SNr stimulation (Takakusaki and Saitoh, 2006). This observation suggests that an increased output from the BG-BS system increases the level of postural muscle tone (hypertonus) by enhancement of the muscle tone excitatory system and reduction of the inhibitory system.

The BG-BS systems would then be responsible for the automatic regulation of postural muscle tone and the rhythmic alternation of limb movements which are associated with volitional and emotional behaviors. It follows that locomotor control by the basal ganglia can be achieved by the descending projections to the brainstem in addition to their loops with the cerebral cortex. In turn, the PPN provides strong excitatory (both glutamatergic and cholinergic) inputs to the midbrain dopaminergic neurons (Futami et al., 1995; Takakusaki et al., 1996). An excitotoxic lesion of the PPN was observed to produce Parkinsonism (Kojima et al., 1997). It is therefore conceivable for the PPN to be a relay center between the cerebral cortex and the spinal cord, acting

as a brainstem motor center for interlimb coordination in locomotion and precise motor behavior (Takakusaki et al., 1996). Moreover the PPN functions as a modulatory center that receives excitatory drive from the cerebral cortex and controls the activity of the thalamus and the basal ganglia, especially the nigral dopamine neurons. It therefore possibly influences cognitive motivational behavior, including motor learning and the reward system (Kobayashi et al., 2002; Matsumura 2005).

3.2. Pathophysiology of gait disturbances in Parkinson disease.

Parkinson disease is characterized by its unique clinical symptoms of akinesia, muscular rigidity, and resting tremor. A histopathological study demonstrated a degeneration of the neurons in the substantia nigra pars compacta (SNc; Forno, 1996). With the presence of dopamine in the striatum the basal ganglia output is well balanced by parallel direct and indirect pathways (Fig.2A). However, the GABAergic output of the basal ganglia is thought to be overactive (Fig.2B; Wichmann and Delong, 2003). Gait disturbance is also a major impediment in this disease. There are delays in gait onset (frozen gait), an increase in the stance phase in step cycles and a decrease in gait velocity. Parkinsonian gait dyskinesia has been considered to be an inability of motor planning and programming at the level of the premotor and supplementary areas of the cerebral cortex (Hanakawa et al. 1999; Morris et al., 1994; Pahapill and Lazano, 2000). However, SNr stimulation altered MLR-induced locomotor patterns which resembled the parkinsonian gait deficiencies. Moreover, SNr stimulation blocked the PPN-induced muscular atonia, indicating that suppression of the muscle tone inhibitory system induces hypertonus (muscle rigidity) by a reduction in inhibitory effects upon α- and γ-motoneurons. From these considerations, a dysfunction of the BG-BS system together with that of the cortico-basal ganglia loop could underlie the pathogenesis of the motor disturbances in Parkinson disease (Fig.2B).

4. Control of locomotor behavior by hypothalamic orexinergic projections.

4.1. Orexinergic modulation of locomotion and postural muscle tone.

In narcoleptic patients and animals, emotional signals elicit a sudden loss of muscle tone (cataplexy; Nishino, 2003). Thus emotional signals may not only induce locomotor behavior in wakefulness but also elicit muscular atonia in narcolepsy. How then do emotional stimuli then elicit muscular atonia in narcolepsy? It has been noted that in human narcolepsy there were reduced numbers of orexin (hypocretin) neurons (Thannickal et al., 2000). Canine narcolepsy is reportedly caused by exon skipping mutations of the orexin-receptor-2 gene (Lin et al., 1999). Orexin neurons are located in the perifornical lateral hypothalamus and project to most brain areas (Peyron et al., 1998), and in particular to the brainstem aminergic and cholinergic nuclei. Orexin neurons are thus likely to regulate vigilance states (Nishino, 2003): they fire at high rates during wakefulness and low rates during REM sleep (Koyama et al., 2003; Mileykovskiy et al, 2005). The orexin neurons also regulate somatomotor control, feeding, and energy balance (Nishino, 2003; Okumura et al., 2001; Sakurai et al., 2002).

The mesopontine tegmentum, including the MLR, PPN and the SNr, is also a major target of the orexinergic system. It was therefore interesting to examine how injections of orexin (60 – 1000 μM, 0.20 – 0.25 μl) into these areas could modulate locomotion and postural muscle tone (Takakusaki et al., 2005). In decerebrate cats, injections of orexin-A into the MLR facilitated locomotion, and those into either the PPN or the SNr suppressed PPN-induced muscular atonia. Because the latter effects were reversed by subsequent injections of bicuculline into the PPN, orexin was considered to activate GABAergic neurons in the PPN and the SNr, which in turn, inhibit cholinergic PPN neurons. It was also observed that an orexin injection into the PPN reduced the coerulospinal excitatory output to motoneurons. These findings suggest that in the

presence of orexin excitability is preferentially higher in the locomotor system and the muscle tone excitatory system than in the atonia system. In contrast, in the absence of orexin inputs to the midbrain the excitability of the atonia system could be preferentially higher than the rhythm generating system and muscle tone excitatory system.

4.2. Implications of pathophysiological mechanisms of narcolepsy.

The pathophysiology of narcolepsy has been intensively described in previous reviews (Nishino, 2003; Siegel, 2004). In our study, as shown in Fig.2C, higher orexinergic and monoaminergic influences enhance the excitability of the locomotor system and the muscle tone excitatory system, but reduce the excitability of the REM sleep generating system (the muscle tone inhibitory system) in a normal awake state. Emotional signals via the limbic and hypothalamic structures (Derryberry and Tucker, 1992; Smith, DeVito, 1984) to the midbrain may increase muscle tone and induce emotional locomotor behavior (Garcia-Rill et al., 2004; Shaikh et al., 1984) (Fig.2C). In the absence of orexin (Fig.2D), the excitability of both the locomotor system and the muscle tone excitatory system would be reduced. The excitability of the REM sleep generating system however, would be enhanced. It should be noted that it is possible that cataplexy is induced by not only reduced activity of the excitatory systems, including the coerulospinal tract, but also by increased activity of the muscle tone inhibitory system. If this is the case, emotional signals could suddenly induce cataplexy in narcolepsy. However narcolepsy patients are alert during atonia because the neocortex is normally active. I propose that orexin may be a determinant for the selection of emotional motor behavior.

The mechanisms of REM sleep behavioral disorders (RBD) may suggest a role for a limbic control of locomotor behavior. Despite the electroencephalographic similarities, the psychological states of wakefulness and REM sleep are obviously

different. The neocortex is active during wakefulness, but the limbic areas are more active than the neocortex during REM sleep (Braun et al., 1997; Marquet, 2000). Such a different activity in the forebrain would be critical for state-dependent motor control. Because of lower orexin and monoamine levels (Koyama et al., 2003; Siegel, 2004), the excitability of the muscle tone inhibitory system would be higher. A higher limbic activity in a normal REM sleep period may thus preferentially excite this system, and result in muscular atonia. However experimental lesions in the muscle tone inhibitory system, such as the PRF (Hendricks et al., 1982) and the medial MRF (Schenkel and Siegel, 1989), have induced “REM without atonia”, which is an animal model of human RBD. Signals through the limbic system may preferentially activate the excitatory system and rhythm generating system via the MLR if motor inhibition is insufficient (Takakusaki et al., 2006). Consequently, hyperactivity of the limbic system during a REM sleep period may induce locomotor behavior, and result in “dream enactment”, as indicated by Morrison (1983).

5. How does the forebrain initiate, integrate and select locomotor behavior?

Locomotion is mostly enabled by a ventral part of the basal ganglia, through the nucleus accumbens, by a pallidal projection to the MLR (Sinnamon, 1993). However, goal-directed locomotor activity requires non-limbic systems. Indeed, motor cortical neurons significantly increased their discharge rate when walking animals had to accurately overcome obstacles (Drew et al., 1996). This accuracy requires a visuomotor gait modification so that a precise foot placement can be achieved (Georgopoulos and Grillner, 1989). Loops involving the cerebral cortex with the basal ganglia and the cerebellum can assist such accurate cognitive operations (Middleton and Strick, 2000).

Visual sensation is particularly critical for gait modification. For example, the deficiency of parkinsonian gait is dramatically overcome if the floor is grid-patterned, or

a transverse-strip is used (Paradoxical gait). Hanakawa et al. (1998) observed by using positron emission tomography (PET) that activities of the left parieto-occipital and right prefrontal cortices were increased during paradoxical gait. The results indicated that the loops are involved in the generation of a *"**volitional and cognitive motor reference**"*. Although memories of volitional behavior require activity of the non-limbic sensorimotor system, unconscious and motivational limbic influences, such as *"**emotional motor references**"* (Fig.2A), are needed to enact any motor plans. So that the limbic system can influence the sensorimotor system, an integrated "***gating function***" has to be operated between the limbic system and non-limbic structures.

Here I refer to a "gating mechanism at the level of the midbrain" on the basis of our recent findings. The midbrain receives excitatory inputs from the cerebral cortex and the limbic system, and inhibitory inputs from the basal ganglia (Fig.1A). The basal ganglia also have neuronal loops with both the motor cortical areas and the limbic structures. Accordingly, emotional signals from the limbic-hypothalamus as well as volitional signals from the cerebral cortex could be modulated by basal ganglia output to the brainstem. Consequently, basal ganglia efferents to both the forebrain and the midbrain may have a role in the selection of volitionally-initiated and emotionally-triggered behavior so that an animal could elicit a variety of locomotor behaviors, depending on the behavioral context. The preference of forebrain structures (cerebral cortex versus limbic system) and that of the brainstem-spinal cord (locomotor system versus inhibitory system) are additionally critical to the selection of state-dependent motor behavior.

Rational gating mechanisms could exist in the forebrain. Nonetheless it has not been elucidated how rational and emotional behaviors are selected at the level of the forebrain between the limbic system and prefrontal cortex depending on the information of past memory and real time working memory (Grillner et al., 1997). Finally I would

like to mention that in humans the “gating mechanisms” at the level of the forebrain may require an understanding of the psychological processes of the conflict between reason and emotion.

ACKNOWLEDGEMENTS

This work is supported by Grants-in-Aid for Scientific Research (C) and Priority Areas "Emergence of Adaptive Motor Function through Interaction between Body, Brain and Environment" from the Japanese Ministry of Education, Culture, Sports, Science and Technology to K.T.

REFERENCES

Braun, A.R., Balkin, T.J., Wesenten, N.J., Carson, R.E., Varga, M., Baldwin, P., Selbie, S., Belenky, G., Herscovitch, P., 1997. Regional cerebral blood flow throughout the sleep-wake cycle; An $H_2{}^{15}O$ PET study. Brain 120,1173-1197

Culebras, A., Moore, J.T., 1989. Magnetic resonance findings in REM sleep behavior disorder. Neurology 39, 1519–1523.

Denny-Brown, D., 1962. The midbrain and motor integration. Proc. R. Soc. Med. 55, 527-538.

Derryberry, D., Tucker, D.M., 1992. Neural mechanisms of emotion. J. Consult. Clin. Psychol. 60, 329–338.

Drew, T., Jiang, W., Kably, B., Lavoie, S., 1996. Role of the motor cortex in the control of visually triggered gait modifications. Can. J. Physiol. Pharmacol. 74, 426-442.

Drew, T, Prentice, S., Schepens, B., 2004. Cortical and brainstem control of locomotion. Prog Brain Res. 143, 251-261.

Forno, L.S. 1996. Neurophysiology of Parkinson's disease. J. Neurophathol Exp. Neurol. 55, 259-272.

Futami, T., Takakusaki, K., Kitai, S.T., 1995. Glutamatergic and cholinergic inputs from the pedunculopontine tegmental nucleus to dopamine neurons in the substantia nigra pars compacta. Neurosci. Res. 21, 331-342.

Garcia-Rill, E., Homma, Y., Skinner, R.D., 2004. Arousal mechanisms related to posture and locomotion: 1. Descending modulation. Prog. Brain Res. 143, 283–290.

Georgopoulos, A.P., Grillner, S., 1989. Visuomotor coordination in reaching and locomotion. Science 245, 1209-1210.

Grillner, S., 1981. Control of locomotion in bipeds, tetrapods, and fish. In: Brooks, V.B. (Ed.), The Nervous System II, Am. Physiol. Soc. Press, Bethesda, pp 1179-1236.

Grillner S., 2003. The motor infrastructure: from ion channels to neuronal networks. Nat. Rev. Neurosci. 4, 573-586.

Grillner, S., Georgopoulos, A.P., Jordan L.M., 1997. Selection and initiation of motor behavior. In: Stein, P.S.G., Grillner, S., Selverson, A.I., Stuart, D.G. (Eds.), Neurons, Networks, and Motor Behavior, MIT Press, Boston, pp. 3-19.

Hanakawa, T., Katsumi, Y., Fukuyama, H., Honda, M., Hayashi, T., Kimura, J., Shibasaki, H., 1999. Mechanisms underlying gait disturbance in Parkinson's disease: a single photon emission computed tomography study. Brain 122, 1271-1282.

Hendricks, J.C., Morrison, A.R., Mann, G.L., 1982. Different behaviors during paradoxical sleep without atonia depend on pontine lesion site. Brain Res. 239, 81–105.

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

Jordan, L.M., 1998. Initiation of locomotion in mammals. Ann. NY Acad.Sci. 16, 860: 83-93.

Kobayashi, Y., Inoue, Y., Yamamoto, M., Isa, T., Aizawa, H., 2002. Contribution of pedunculo- pontine tegmental nucleus neurons to performance of visually guided

saccade tasks in monkeys. J. Neurophysiol. 88, 715-731.

Kojima. J., Yamaji. Y., Matsumura. M., Nambu. A., Inase. M., Tokuno. H., Takada. M., Imai. H., 1997. Excitotoxic lesions of the pedunculopontine tegmental nucleus produce contralateral hemiparkinsonism in the monkey. Neurosci. Lett. 226, 111-114.

Koyama, Y., Takahashi, K., Kodama, T., Kayama, Y., 2003. State-dependent activity of neurons in the perifornical hypothalamic area during sleep and waking. Neuroscience 119, 1209-1219.

Lin, L., Faraco, J., Li, R., Kadotani, H., Rogers, W., Lin, X., Qiu, X., de Jong, P.J., Nishino, S., Mignot, E., 1999. The sleep disorder canine narcolepsy is caused by a mutation in the hypocretin (orexin) receptor 2 gene. Cell 98, 365-376.

Maquet P., 2000. Functional neuroimaging of normal human sleep by positron emission tomography. J. Sleep Res. 9, 207–231

Masdeu, J.C., Alampur, U., Cavaliere, R., Tavoulareas, G., 1994. Astasia and gait failure with damage of the pontomesencephalic locomotor region. Ann. Neurol. 35, 619-621.

Matsumura, M., 2005. The pedunculopontine tegmental nucleus and experimental parkinsonism. J. Neurol. 252, Suppl 4, IV/5–IV/12.

Middleton, F.A., Strick, P.L., 2000. Basal ganglia and cerebellar loops: motor and cognitive circuits. Brain Res. Rev. 31, 236–250.

Mileykovskiy, B.Y., Kiyashchenko, L..I, Siegel, J.M, 2005. Behavioral correlates of activity in identified hypocretin/orexin neurons. Neuron 46, 787-798.

Mori, S., 1987. Integration of posture and locomotion in acute decerebrate cats and in awake, free moving cats. Prog. Neurobiol. 28, 161-196.

Moriizumi, T., Nakamura, Y., Tokuno, H., Kitao, Y., Kudo, M., 1988. Topographic projections from the basal ganglia to the nucleus tegmenti pedunculopontinus pars compacta of the cat with special reference to pallidal projections. Expl. Brain Res. 71, 298–306.

Morris, M.E., Iansek, R., Matyas, T.A., Summers, J.J., 1994. The pathogenesis of gait hypokinesia in Parkinson's disease. Brain 117, 1169-1181.

Morrison, A.R., 1983. A window on the sleeping brain. Sci. Am. 248, 94–102.

Nishino, S., 2003. The hypocretin/orexin system in health and disease. Biol. Psychiat. 54, 87–95.

Okumura, T., Takeuchi, S., Motomura, W., Yamada, H., Egashira, Si S., Asahi, S., Kanatani, A., Ihara, M., Kohgo, Y., 2001, Requirement of intact disulfide bonds in orexin-A-induced stimulation of gastric acid secretion that is mediated by OX1 receptor activation. Biochem. Biophys. Res. Commun. 280, 976-981.

Pahapill P.A., Lozano A.M., 2000. The pedunculopontine nucleus and Parkinson's disease. Brain 123, 1767-1783.

Peyron, C., Tighe, D.K., van den Pol, A.N., de Lecea, L., Heller, H.C., Sutcliffe, J.G., Kilduff, T.S., 1998. Neurons containing hypocretin (orexin) project to multiple neuronal systems. J. Neurosci. 18, 9996-10015.

Saitoh, K., Hattori, S., Song, W.J., Isa, T, Takakusaki, K., 2003. Nigral GABAergic inhibition upon cholinergic neurons in the rat pedunculopontine tegmental nucleus.

Eur. J. Neurosci. 18, 879-886.

Sakurai, T., 2002. Roles of orexins in regulation of feeding and wakefulness. Neuroreport 13: 987-995.Shik, M.L,, Severin, F,V., Orlovskii, G.N., 1966. Control of walking and running by means of electric stimulation of the midbrain. Biofizika 11, 659-666.

Schenkel, E., Siegel, J.M., 1989. REM sleep without atonia after lesions of the medial medulla. Neurosci. Lett. 98, 159–165.

Shaikh, M.B., Brutus, M., Siegel, B.E., Siegel, A., 1984. Differential control of aggression by the midbrain. Expl. Neurol. 83, 436–442.

Siegel, J.M., 2004. Hypocretin (orexn): Role in normal behavior and neuropathology. Ann. Rev. Psychol. 55, 125–148.

Sinnamon, H.M., 1993. Preoptic and hypothalamic neurons and initiation of locomotion in the anesthetized rat. Prog. Neurobiol. 41, 323-344.

Smith, O.A., DeVito, J.L., 1984. Central neural integration for the control of autonomic responses associated with emotion. Ann. Rev. Neurosci. 7, 43–65.

Spann, B.M., Grofova, I., 1991. Nigro-pedunculopontine projection in the rat: an anterograde tracing study with Phaseolus Vulgaris-Leucoagglutinin (PHA-L). J. Comp. Neurol. 311, 375–388.

Takakusaki K, Habaguchi T., Saitoh K, Kohyama, J., 2004a. Changes in the excitability of hindlimb motoneuros during muscular atonia induced by stimulating the pedunculopontine tegmental nucleus in cats. Neuroscience 124, 467-480.

Takakusaki, K., Saitoh, K., Harada, H., Okumura, T., Sakamoto, T., 2004a. 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 124, 207-220.

Takakusaki, K., Habaguchi. T., Ohinata-Sugimoto, J., Saitoh, K., Sakamoto, T., 2003b. 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 119, 293-308.

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

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

Takakusaki, K., Saitoh, 2006. Synaptic mechanisms acting on motoneurons with reference to the basal ganglia control of locomotion. J. Physiol. Sci. 56(Suppl), S93.

Takakusaki K, Saitoh K, Harada H, Kashiwayanagi M., 2004b. Role of basal ganglia – brainstem pathways in the control of motor behaviors .Neuroscience Research. 50, 137-151

Taksakusaki, K., Saitoh, K., Nonaka, S., Okumura, T., Miyokawa, N., Koyama, Y., 2006. Neurobiological basis of state-dependent control of motor behavior. Sleep Biol. Rhyth. 4, 87-104.

Takakusaki, K., Shimoda, N., Matsuyama, K., Mori, S., 1994. 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. Expl. Brain Res. 99, 361-374.

Takakusaki, K., Takahashi, K., Saitoh, K., Harada, H., Okumura, T., Kayama, Y., Koyama, Y., 2005. Orexinergic projections to the cat midbrain mediate alternation of emotional behavioural states from locomotion to cataplexy. J. Physiol. 568, 1003-1020, 2005

Takakusaki, K., Shiroyama, T., Yamamoto, T., Kitai, S.T.., 1996. Cholinergic and noncholinergic tegmental pedunculopontine projection neurons in rats revealed by intracellular labeling. J. Comp. Neurol. 371, 345-361.

Thannickal, T.C., Moore, R,Y,, Nienhuis, R., Ramanathan, L., Gulyani, S, Aldrich, M,, Cornford, M,, Siegel, J.M., 2000. Reduced number of hypocretin neurons in human narcolepsy. Neuron 27, 469-474.

Villablanca J, Marcus R., 1972. Sleep-wakefulness, EEG and behavioral studies of chronic cats without neocortex and striatum: the 'diencephalic' cat. Arch. Ital. Biol. 110, 348-382.

Villablanca, J.R., Olmstead, C.E., 1982. The striatum: a fine tuner of the brain. Acta. Neurobiol. Exp. 42, 227-299.

Wichmann, T., Delong M.R., 2003. Pathophysiology of Parkinson's disease: the MPTP primate model of the human disorder. Ann. NY. Acad. Sci. 991, 199-213.

FIGURE LEGENDS

Figure 1. Possible framework of forebrain control of locomotor behavior

A: Neural connections between forebrain and hindbrain structures involved in the control of locomotor behavior. Open and filled lines are possibly excitatory and inhibitory, respectively. Forebrain structures such as the cerebral cortex and the limbic-hypothalamic system provide glutamatergic excitatory drives to the brainstem motor centers, including the midbrain locomotor region (MLR) and muscle tone inhibitory region in the pedunculopontine tegmental nucleus (PPN). The neocortical projections provide a motor reference depending on (visuomotor) cognitive sensory inputs (Volitional and Cognitive Motor References). On the other hand, the limbic system and hypothalamus provide an emotional reference which can be generated, depending on both external stimuli and internal (visceral) information. In contrast, the basal ganglia provide GABAergic inhibitory drives to the brainstem. Therefore, the regulation (initiation, integration and selection) of locomotion and associated postural changes can be achieved by the balance between the excitatory (neocortex and limbic-hypothalamus) and inhibitory (basal ganglia) inputs to the brainstem. See text for further detailed explanations.

B: Changes in intracellular activity of soleus motoneurons in a decerebrate cat. (a) Repetitive electrical stimulation of the MLR (a) first depolarized the membrane and generated rhythmic membrane oscillations (fictive locomotion). (b) Stimulation of the ventrolateral part of the PPN stopped firing and hyperpolarized the membrane. The inset figure illustrates antidromic spikes of this motoneuron (From Takakusaki et al. 2004a.)

C: (a) Effective stimulus sites in the substantia nigra (SNr) and the mesopontine tegmentum for controlling locomotion (open squares) and muscle tone (closed squares). (b) Effective stimulus sites for evoking locomotion (open circles) and inhibiting muscle tone (closed circles). See text for further explanations.

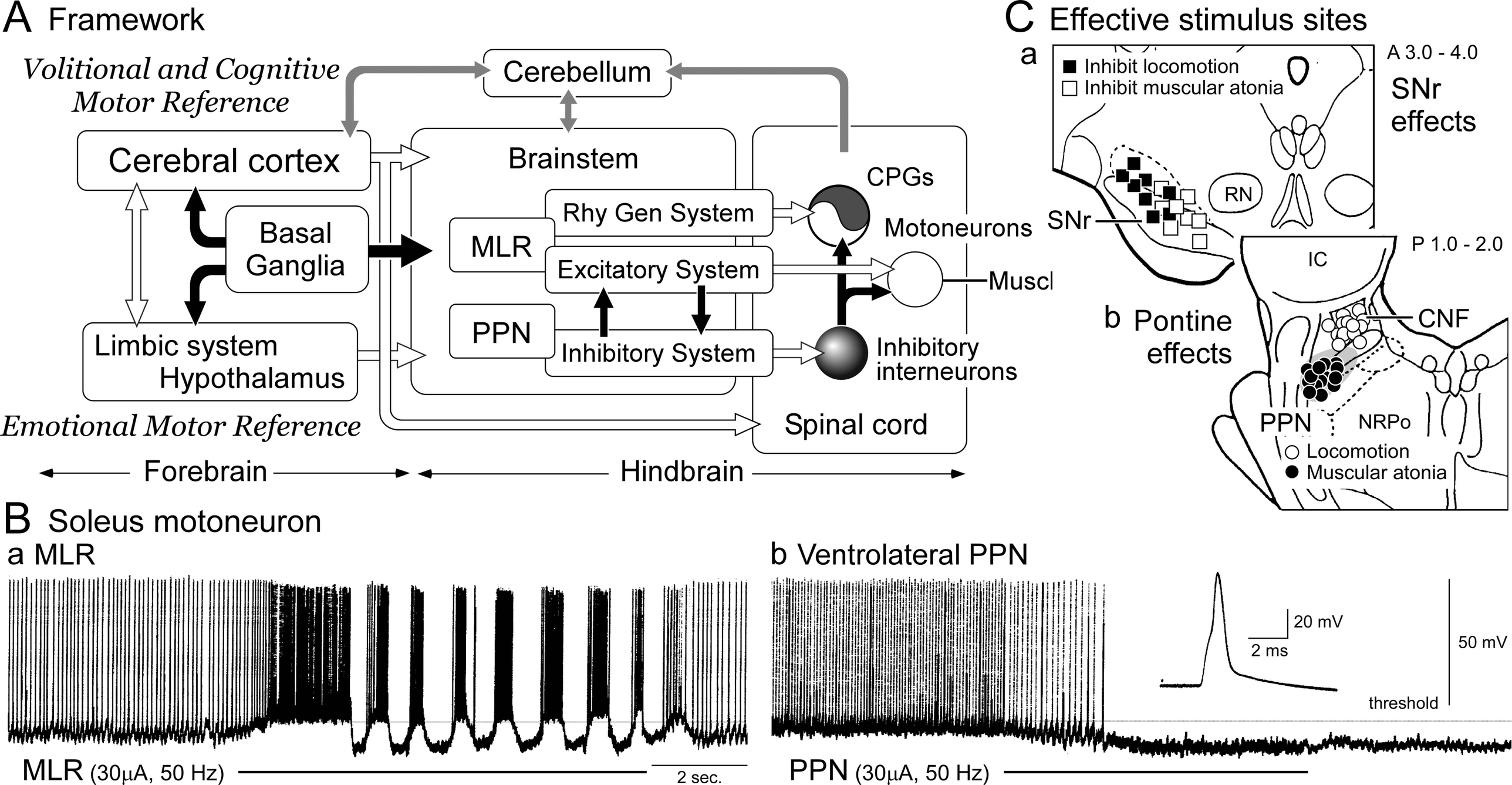
Figure 2. Simplified models of forebrain control of locomotor behavior

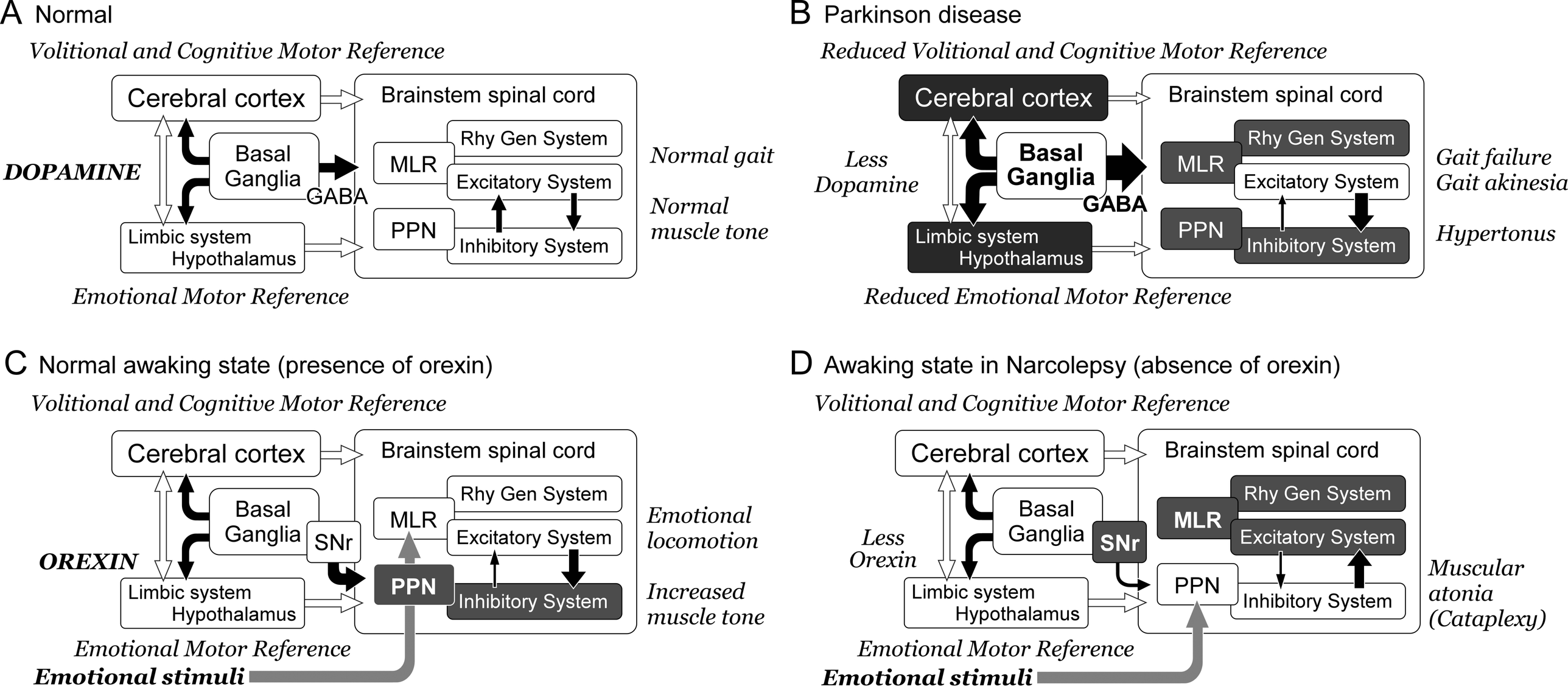
A: Normal. A dopaminergic influence maintains an appropriate balance of excitatory and inhibitory output from the forebrain to the brainstem.

B: Parkinson's disease. Loss of dopamine may increase the inhibitory output from the basal ganglia, which then inhibits the activity of the forebrain (neocortex and limbic system) and the brainstem. Excessive direct inhibition upon the MLR and indirect inhibition through the motor cortical areas induces gait failure and gait akinesia. Also excessive inhibition upon the PPN inhibits the activity of muscle tone inhibitory system and enhances the activity of muscle tone excitatory system, resulting in hypertonus (rigidity).

C: Normal awaking state and effects of orexinergic input to the midbrain. Orexinergic input to the MLR facilitates a rhythm generating system and muscle tone excitatory system. Input to the PPN and the SNr inhibits the muscle tone inhibitory system via an activation of GABAergic neurons which inhibit cholinergic PPN neurons. Therefore, in the presence of orexin, emotional stimuli through the limbic system to the brainstem may preferentially elicit locomotion or muscular augmentation (emotional behavior).

D: Awaking state in narcolepsy. Because of an orexin deficiency, the background excitability would be higher in the muscle tone inhibitory system than in the rhythm generating system and muscle tone excitatory system. Consequently, the emotional stimuli preferentially activate the muscle tone inhibitory system, resulting in muscular atonia (cataplexy). In A–D, the open and filled arrows indicate excitatory and inhibitory effects, respectively. Thick and thin arrows indicate that the output is higher and lower, respectively. Structures which are considered to have a lower excitability are shown by filled (dark) symbols.


A Framework
Volitional and Cognitive Motor Reference
Cerebellum
Cerebral cortex
Brainstem
CPGs
Basal Ganglia
Rhy Gen System
MLR
Motoneurons
Excitatory System
Muscl
PPN
Inhibitory System
Inhibitory interneurons
Limbic system Hypothalamus
Spinal cord
Emotional Motor Reference
Forebrain
Hindbrain
C Effective stimulus sites
a
Inhibit locomotion
Inhibit muscular atonia
A 3.0 - 4.0
SNr effects
RN
SNr
IC
P 1.0 - 2.0
b Pontine effects
CNF
PPN
NRPo
Locomotion
Muscular atonia
B Soleus motoneuron
a MLR
MLR (30μA, 50 Hz)
2 sec.
b Ventrolateral PPN
20 mV
2 ms
50 mV
threshold
PPN (30μA, 50 Hz)


A Normal
Volitional and Cognitive Motor Reference
Cerebral cortex
Brainstem spinal cord
Basal Ganglia
DOPAMINE
GABA
MLR
Rhy Gen System
Excitatory System
PPN
Inhibitory System
Limbic system Hypothalamus
Normal gait
Normal muscle tone
Emotional Motor Reference
B Parkinson disease
Reduced Volitional and Cognitive Motor Reference
Cerebral cortex
Brainstem spinal cord
Less Dopamine
Basal Ganglia
GABA
MLR
Rhy Gen System
Excitatory System
PPN
Inhibitory System
Limbic system Hypothalamus
Gait failure
Gait akinesia
Hypertonus
Reduced Emotional Motor Reference
C Normal awaking state (presence of orexin)
Volitional and Cognitive Motor Reference
Cerebral cortex
Brainstem spinal cord
Basal Ganglia
SNr
OREXIN
MLR
Rhy Gen System
Excitatory System
PPN
Inhibitory System
Limbic system Hypothalamus
Emotional locomotion
Increased muscle tone
Emotional Motor Reference
Emotional stimuli
D Awaking state in Narcolepsy (absence of orexin)
Volitional and Cognitive Motor Reference
Cerebral cortex
Brainstem spinal cord
Less Orexin
Basal Ganglia
SNr
MLR
Rhy Gen System
Excitatory System
PPN
Inhibitory System
Limbic system Hypothalamus
Muscular atonia (Cataplexy)
Emotional Motor Reference
Emotional stimuli