Role of basal ganglia – brainstem pathways in the control of motor behaviors

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Abstract

Here we review a role of a basal ganglia-brainstem system throughout the mesopontine tegmentum in the control of various types of behavioral expression. First the basal ganglia-brainstem system may contribute to an automatic control of movements, such as rhythmic limb movements and adjustment of postural muscle tone during locomotion, which occurs in conjunction with voluntary control processes. Second, the basal ganglia-brainstem system can be involved in the regulation of awake-sleep states. We further propose the possibility that the basal ganglia-brainstem system is responsible for the integration of volitionally-guided and emotionally-triggered expression of motor behaviors. It can be proposed that dysfunction of the basal ganglia-brainstem system together with that of cortico-basal ganglia loop underlies the pathogenesis of behavioral disturbances expressed in basal ganglia dysfunction.

1. Introduction

Basal ganglia disorders are manifested by an inability to initiate and terminate voluntary movements in a certain behavioral context, an inability to suppress involuntary movements, an abnormality in the velocity and the amount of movement, and an abnormal muscle tone (Obeso et al., 1997; Saint-Cyr et al., 1995). Gait disturbances are also a major impediment for Parkinsonian patients (Murray et al., 1978; Morris et al., 1994). Marsden (1982) hypothesized, in his lecture titled as "The mysterious motor function of the basal ganglia", that "the basal ganglia are responsible for the autonomic execution of learned motor plans". This hypothesis was derived from his careful insight into the consideration of the motor disturbances in basal ganglia disorders. Specifically, primary clinical deficit in Parkinson disease is slowness of movement, particularly when actions are volitional (Marsden, 1989).

The current understanding is that the basal ganglia and cerebellar loops with the motor areas of the cerebral cortex are involved in the control of voluntary movements (Middleton and Strick, 2000). Additional evidence indicates that the basal ganglia contribute to the planning and execution of voluntary movements via a series of parallel basal ganglia thalamocortical loops (Alexander and Crutcher, 1990; Delong, 1990; Turner and Anderson, 1997). But how the basal ganglia control muscle tone and gait performance is still unclear. The basal ganglia outflow is also directed to some of the motor networks in the brainstem (Inglis and Winn, 1995; Hikosaka et al., 2000; Takakusaki et al., 2003a) where fundamental neuronal networks for controlling muscle tone and locomotor movements (Garcia-Rill, 1991; Grillner, 1981; Mori, 1987; Rossignol, 1996) are located. Therefore, it can be postulated that the basal ganglia projections to the brainstem networks contribute to the control of postural muscle tone and locomotion.

Here, we propose that the basal ganglia outputs directly toward to the brainstem, together with those via the thalamocortical loops, are involved in the integrative process of

postural muscle tone and locomotion. This article is roughly divided into three parts. First, we introduce basic neural substrates involved in the control of locomotion and muscle tone, and their regulation by the GABAergic output from the basal ganglia. In the second part, we propose a new concept for understanding basal ganglia control of movements with special reference to the role of the basal ganglia-brainstem (BG-BS) systems in the integration of postural muscle tone and locomotion. This proposition was largely based on our recent experimental evidence which was obtained in decerebrate animals (Takakusaki et al., 2003a, 2004b, 2004c). The issues dealt within the third part are not limited to the role of the BG-BS systems in the motor control but are of more global importances for brain function in general. The idea, which we provide here, may assist understanding the mechanisms of disturbances of both motor and non-motor functions in basal ganglia disorders.

2.   BG-BS Systems and Motor Control

2-1; General schema of the basal ganglia control of movements

Voluntary movements are always associated with automatic control processes that are performed unconsciously (Grillner and Wallen, 2004). For example, initiation and termination of locomotion and avoiding obstacles during locomotion are volitional processes that require accurate control (Georgopoulos and Grillner, 1989). Similarly, the subject is largely unaware of the automatic control of rhythmic limb movements, postural muscle tone, and the postural reflexes that accompany locomotion (Takakusaki et al., 2004a). The fact that each such aspect of locomotion is seriously impaired in Parkinsonian patients (Morris et al., 1994; Murray et al., 1978) indicates that the basal ganglia must play a crucial role in integrating the volitional and automatic aspects of the descending control of posture and movement. Hikosaka et al. (2000) propose that the basal ganglia have two

ways to control movements using two kinds of output; one is via the thalamocortical networks, and the other is a control over brainstem motor networks. These outputs from the basal ganglia are schematically illustrated in Fig. 1. The basal ganglia output to the cerebral cortex can be responsible for the volitional control processes of movements. Particular patterns of movements such as such as saccade (Hikosaka et al., 2000; Hikosaka and Wurtz, 1983a, 1983b, 1983c; Isa, 2002; Sparks, 2002), mastication (Scott et al., 2003), vocalization (Dusterhoft et al., 2000), swallowing (Amirali et al., 2001) and locomotion (Grillner, 2003; Rossignol, 1996) are thought to be generated by specific neuronal networks in the brainstem and spinal cord. Basal ganglia output to the networks for these movements in the brainstem and the spinal cord could be involved in the achievements of automatic control processes that accompany the voluntary movements.

In this article, we emphasize the importance of GABAergic basal ganglia projections, via the SNr, toward to the mesopontine tegmentum (Inglis and Winn, 1995; Hikosaka et al., 2000; Takakusaki et al., 2003a) in the control of postural muscle tone and locomotion, since muscle tone inhibitory region in the pedunculopontine tegmental nucleus (PPN; Lai and Siegel, 1990; Takakusaki et al., 2003a) and the midbrain locomotor region (MLR; Garcia-Rill, 1991; Grillner et al., 1997; Rossignol, 1996; Takakusaki et al., 2003a) are located in the mesopontine tegmentum. Therefore we first refer to the basic architectures of locomotor system and muscle tone control system before considerations of roles of BG-BS system in the control of postural muscle tone and locomotion.

2-1; Basic Architectures of Locomotor System and Muscle Tone Control System

It is established that repetitive stimulation of the MLR evokes controlled locomotion in decerebrate preparations (Fig.2A). Decerebrate cats maintain reflex standing posture due to tonic contractions of postural muscles (decerebrate rigidity). Stimulation of

the MLR first increased muscle tone and initiated alternating hindlimb stepping movements. Then the stepping movements developed to locomotor movements when treadmill was started to move (Fig.2Ba). Moreover, microinjection of N-methyl-D-aspartic acid (NMDA) into the MLR increased muscle tone (Fig.2Ca), and initiated locomotion on the moving treadmill belt (Fig.2Cb). These findings support previous notion that signals from cells in the MLR released the activities of rhythm generating systems in addition to muscle tone facilitatory systems (Mori et al. 1987). In the PPN, both cholinergic and non-cholinergic neurons are present (Span and Grofova, 1992). Garcia-Rill and his colleagues (Garcia-Rill, 1991; Skinner et al., 1990) describe that an activation of PPN cholinergic neurons is required to initiate locomotion. However, most studies including our study (Takakusaki et al., 2003a) demonstrate that the MLR is mainly located in the area dorsomedial to the PPN but not within the PPN (Fig.2D). The area rather corresponds to the cuneiform nucleus (CNF) where cholinergic neurons are rarely distributed (Fig.2E).

Figure 3A illustrates our current perception of the locomotion executing system which is based on our results in addition to previous works (Grillner, 1981; Mori, 1987; Rossignol, 1996). There at least two major pathways descend from the MLR. One is via the medial medullary reticulospinal tract and the other is via the pontomedullary locomotor strip (PMLS). Both pathways activate the central pattern generators (CPG) in spinal cord, whose output generates locomotor rhythms. Signals from the MLR may also activate muscle tone facilitatory systems such as the raphespinal and coerulospinal tracts (Lai and Siegel, 1990; Mori, 1987). A cortical input to the MLR is conceivably mediated via polysynaptic connections through the subthalamic locomotor region (SLR; Rossignol, 1996). A clinical report shows a patient with a lesion in the dorsolateral mesopontine tegmentum could not stand and walk (Masdue et al., 1994). Thus an MLR is also reality in the mesopontine tegmentum of the human

The neural architecture of the muscle tone inhibitory system is perceived somewhat differently among researchers. However there is a general agreement that cholinoceptive pontomedullary reticular formation neurons excite reticulospinal neurons in the medullary inhibitory region of Magoun and Rhines (1946), which corresponds to the nucleus reticularis gigantocellularis, the nucleus reticularis magnocellularis and the nucleus reticularis paramedianus (Chase et al., 1986; Lai and Siegel, 1988, 1991; Takakusaki et al., 2001, Habaguchi et al., 2002). These provide postsynaptic inhibitory effects upon motoneurons directly or via inhibitory interneurons (Chase and Morales, 1990; Takakusaki et al., 2001, 2003b). A similar action is induced from the ventrolateral part of the PPN (Takakusaki et al., 2003a, 2004c). Either electrical or chemical stimulation applied to the ventrolateral PPN in decerebrate cats suppressed postural muscle tone (Fig.2Bb and Cc). Cholinergic neurons were densely distributed in the optimal stimulus sites (Fig.2D and E), indicating that the inhibitory effects are mediated by cholinergic PPN neurons. Figure 3B shows a possible architecture of the muscle tone inhibitory system. PPN stimulation may activate cholinoceptive pontine reticular formation (PRF) neurons (Lai et al., 1993; Mitani et al., 1988), which, in turn, excite medullary reticulospinal neurons and spinal interneurons to inhibit α-motoneurons. Possibly suppressed in parallel are γ-motoneurons and interneurons intercalated in reflex pathways (Takakusaki et al., 2001, 2003b). Monoaminergic systems such as the coerulospinal (Fung and Barnes, 1981) and raphespinal (Sakai et al. 2000) tracts are considered as muscle tone facilitatory systems. There are serotonergic projections to the PPN (Honda and Semba, 1994) and to the medial PRF (Semba, 1993). The former likely inhibits mesopontine cholinergic neurons (Leonald and Llinás, 1994), and the latter reduces the activity of the inhibitory system (Takakusaki et al., 1993, 1994). In contrast, the inhibitory system suppresses the activity of the

coerulospinal tract (Mileykovskiy et al., 2000). Thus muscle tone can be regulated by a counterbalance between the inhibitory and the facilitatory systems.

2-2; BG-BS Systems in the Control of Muscle Tone and Locomotion

In rats (Beckstead et al., 1979; Spann and Grofova, 1991) and cats (Moriizumi et al., 1988) the mesopontine tegmentum receives efferents of the basal ganglia particularly from the SNr. The nigrotegmental efferents use GABA as a neurotransmitter and have terminals preferentially on non-cholinergic neurons rather than cholinergic neurons (Grofova and Zhou, 1998). Saitoh et al, (2003) demonstrated that stimulation of the SNr induced monosynaptic IPSPs in PPN neurons *in vitro* rat brainstem slice. Because the IPSP was diminished by an application of bicuculline, one of $GABA_A$ receptor antagonists, the IPSP was considered to be mediated by GABAergic projections. A single-cell RT-PCR amplification technique revealed that approximately 30 % neurons were cholinergic in nature. These findings suggest that not only non-cholinergic neurons but also cholinergic neurons in the PPN receive GABAergic efferents from the SNr.

How does the GABAergic nigrotegmental projection control locomotion and muscle tone? This was examined in decerebrate cats with the striatum, thalamus and cerebral cortex removed, but the SNr preserved (Fig.4A). An injection of bicuculline into the MLR also elicited locomotion on a moving treadmill (Fig.4Ba). On the other hand, microinjection of bicuculline into the ventrolateral PPN inhibited the locomotor movements along with suppression of postural muscle tone (Fig.4Bb). These findings suggest that GABAergic efferents to the PPN and the MLR conceivably suppress the activity of muscle tone inhibitory system and locomotion executing system, respectively.

Next we examined how SNr stimulation altered the MLR/PPN-induced movements. Stimulation of the SNr alone did not alter muscular activity (Fig. 4Ca).

However, conditioning stimuli applied to the lateral part of the SNr attenuated and blocked the PPN-induced muscle tone suppression (Fig. 4Cb). In addition, stimuli applied to the medial part of the SNr at a low strength reduced the number of MLR-activated step cycles, increased the duration of the stance phase, and disrupted the rhythmic alternation of limb movements (Fig.4D). Stimulation of the SNr at a higher strength eventually stopped MLR-activated locomotion. Furthermore, the onset of the locomotion was delayed by the SNr stimuli of progressively increasing strength. Thus the nigrotegmental projection affects both the steady state (e.g., postural control and rhythmic limb movements) and dynamic state (e.g., initiation and termination) of locomotion. Accordingly, our opinion is that the basal ganglia control postural muscle tone and locomotion by a combined inhibition/disinhibition of both the muscle tone inhibitory system and the locomotion executing system via the GABAergic nigrotegmental projections.

Moreover GABAergic nigrotegmental projections have a partial functional topography: a lateral and medial SNr, for regulation of postural muscle tone and locomotion, respectively (Takakusaki et al., 2003a). Such a parallel organization of the nigrotegmental projections may be capable of controlling locomotion and muscle tone independently. It follows that a variety of locomotor behaviors with various step cycles and various levels of muscle tone could be produced depending on the magnitude of inhibitory effects from the functionally segregated nigrotegmental (medial SNr-MLR and lateral SNr-PPN) projections.

3. Concept for Understanding BG-BS Systems' Involvement of Motor Control

In this section, we first introduce our concept for understanding how the basal ganglia achieve an integration of the volitional and automatic control of movement on the basis of the results and viewpoints described above. On the other hand, mechanisms of saccadic eye movements through pathways from the basal ganglia to the superior colliculus

(SC) have been studied best among BG-BS systems, in particular, by Hikosaka and his co-workers (Hikosaka, 1989; Hikosaka and Wurz, 1983a, 1983b, 1983b; Hikosaka et al., 2000; Sato and Hikosaka, 2002). Thus, in the last part of this section, we point out the similarities and differences between these two concepts

3-1. Concept for Understanding BG-BS systems in the control of postural muscle tone and locomotion

There are multiple cortico-basal ganglia loops with various areas of the cerebral cortex which are concerned with different aspects of motor behavior that requires volition, cognition and attention (Brooks, 1995; Middleton and Strick, 2000) (Fig.5A). The majority of motor cortical neurons significantly altered their discharge properties when a walking subject has to overcome obstacles accurately (Drew et al., 1996). This accuracy requires a precise visuomotor coordination (Georgopoulos and Grillner, 1989). Thus, cortical processing is required for volitional aspects of locomotor movements. Cortico-basal ganglia loop can help serve this purpose. In contrast, a BG-BS system seems required for the automatic regulation of postural muscle tone and rhythmic limb movements during locomotion. The motor cortices have projections to the PPN (Matsumura et al., 2000) and to the pontomedullary reticular formation (Matsuyama and Drew 1997). Therefore the muscle tone control system and the locomotor system can be controlled, in parallel, by a combined input to the brainstem of net inhibition from the basal ganglia, and net excitation from the motor cortex (Fig. 5A).

Given the above consideration, the motor cortical neurons that receive basal ganglia output may control the velocity and the amount of voluntary movement (ordinate on the left of the graph in Fig.5B; Turner and Anderson, 1997). GABAergic inputs from the SNr to the MLR reduced the drive from the MLR to the CPG in spinal cord, resulting in

disrupted the activity of locomotor pattern generator at the level of spinal cord (Fig. 4D).

Thus, a basal ganglia efferent to the MLR may control the locomotor pattern (ordinate on

the right). In addition, a basal ganglia efferent to the PPN may determine the level of

muscle tone via the muscle tone control systems (abscissa). Because the basal ganglia

output is variable in a normal condition, the degree of freedom for the amount and the

velocity of movement, the locomotor velocity, and the muscle tone, can be large. Each

parameter can take any of the coordinates within the frame in Fig.5B. However,

GABAergic basal ganglia output is thought to be overactive in Parkinson disease

(Wichmann and Delong, 1996, 2003). An excessive GABAergic inhibition upon

thalamocortical neurons may decrease the velocity and amount of movement (bradykinesia

and hypokinesia, respectively). An increase in basal ganglia inhibition, together with a

decrease in cortical excitation of the PPN, may increase the level of muscle tone

(hypertonus). Similarly, an excessive inhibition of the MLR and a decrease in cortical

excitation of the brainstem reticular formation may elicit gait failure. Additionally, less

activity of the premotor cortex may disturb the motor programming required for precise

gait control (Hanakawa et al. 1999; Pahapill and Lazano, 2000). As a result, the degree of

freedom for each movement would be restricted, and the frame will be smaller and move to

the upper right (Fig.5Ca).

Gait disturbances, including delays in gait onset (frozen gait), an increase in the

stance phase in locomotor cycles and a decrease in locomotor velocity, are observed in

Parkinsonian patients (Morris et al., 1994; Murray et al., 1978; Pahapill and Lazano, 2000).

Because these gait failure resemble the locomotor pattern induced by SNr stimulation

(Takakusaki et al., 2003a), we consider that a dysfunction of the BG-BS system is the

primary basis for Parkinson disease-induced gait impairments. Moreover, we propose that

muscular rigidity (hypertonus), which is one of the most prominent symptoms of Parkinson

disease, can be a result of inhibition of the muscle tone inhibitory system (Fig.2B). Namely, muscular rigidity can be interpreted in terms of loss of inhibition to α- and γ-motoneurons.

In contrast, a reduction of output from the basal ganglia in Huntington's chorea may increase movement (hyperkinesias) and decrease muscle tone (hypotonus). The frame, which indicates the degree of freedom for movement, would be restricted and move to the lower left for this disease (Fig.5Cb). From these considerations, we suggest that a BG-BS contributes to an automatic control of movement that occurs in conjunction with voluntary control processes. Moreover, the output of the basal ganglia would determine the degree of freedom of each movement, and a restriction of the degree of freedom could exist in the background of Parkinson and Huntington diseases. We suggest that dysfunction of the BG-BS system together with that of cortico-basal ganglia loop underlies the pathogenesis of motor disturbances in these basal ganglia diseases.

Dystonia is a syndrome characterized by abnormal posturing, muscle spasms, and tremor due to involuntary co-contraction of muscle agonists and antagonists. Dystonia can be task specific, patients only developing co-contraction when performing skilled movements such as writing (Van der Kamp et al., 1989). Using positron emission tomography, inappropriate overactivity of the basal ganglia projections to premotor and dorsal prefrontal cortex has been observed in idiopathic and acquired dystonia (Brooks, 1995). However activities of primary sensorimotor and caudal premotor cortices are rather attenuated (Hutchins et al., 1988). Although alterations of noradrenaline and dopamine levels in brainstem structures have been reported in two cases (Hornykiewicz et al., 1986), most studies have found no such abnormalities in the brainstem. These evidences suggest that activity of the BG-BS system and that of cortico-basal ganglia loop are controlled separately in this disease.

3-2. Current Concept for the Basal Ganglia Control of Saccadic Eye Movements

The basal ganglia control saccadic eye movements (saccades) through their connections to the superior colliculus (SC) (Chevalier and Deniau, 1990; Chevarier et al., 1984; Hikosaka and Wurtz, 1983a, 1983b, 1983b). Figure 6A shows basic neural connections involved in the generation of saccade. The SC receives convergent inputs from the cerebral cortex (Hikosaka et al., 2000; Pierrot-Deseilligny et al., 2004) and the basal ganglia (Anderson and Yoshida, 1980; Chevarier et al., 1984). To make a saccade to an object purposefully, appropriate signals must be selected out of the cortical inputs, in which the basal ganglia play a crucial role.

There are two parallel mechanisms in the basal ganglia (Fig.6A), direct and indirect pathways (Alexander and Crutcher, 1990; Delong, 1990). With their high background activity, GABAergic SNr neurons inhibit SC output neurons tonically, thus preventing unnecessary saccades (Fig.6B, 6Cb). The direct pathway from the caudate nucleus (CD) to the SNr removes this sustained inhibition, resulting in a disinhibition of the SC neurons. Namely, phasic activity of GABAergic output neurons in the CD, which are mostly silent (Fig.6B), interrupts the tonic SNr-SC inhibition, thus allowing a saccade to occur (Hikosaka, 1989). The basal ganglia have another mechanism (indirect pathway), involving the external segment of the globus pallidus (GPi) and the subthalamic nucleus (STN), with which the SNr-SC inhibition can further be enhanced (Fig.6A, 6Ca). Excitatory cortical input to the STN may contribute to the further enhancement of SNr-SC inhibition (Fig. 6A, hyperdirect pathway; Nambu et al. 2002). Therefore, direct (CD-SNr) and indirect pathways (CD-GPe -STN-SNr) have an opposite effects on SNr-SC system. Hikosaka et al. (2000) propose that two modes of basal ganglia action, *"focusing"* and *"sequencing"* of basal ganglia signals, are produced by the interaction of the two opposing effects upon SNr neurons (Fig.6D). Simultaneous interaction of the two pathways may produce more selective information and enhance the spatial contrast of neural signals of

the target systems (*focusing*; Fig.6Da). However, sequential interaction of the pathways may produce switching of behavior from the suppression of movement (when the indirect pathway is dominant) to the initiation of movement (when the direct pathway is dominant) (*sequencing*; Fig.6Db). In this mode, the effect would enhance the temporal contrast.

Accordingly, current concept for the basal ganglia control of saccade can be summarized as follows. First, key mechanisms are an enhancement of tonic inhibition and a release from the inhibition (disinhibition). The second mechanisms are focusing and sequencing. These two modes can be produced by an interaction of direct and indirect pathways. The above mechanisms may act on brainstem networks in addition to thalamocortical networks (Hikosaka et al., 2000).

3-3. Comparisons of Two Concepts

Similar to the basal ganglia control of saccade, disinhibition and enhancement of the inhibition can be also key mechanisms for the basal ganglia control of postural muscle tone and locomotion. Because muscle tone inhibitory region in the PPN and the MLR, as well as the SC, receive GABAergic input from the SNr, locomotor system and muscle tone control system may be regulated by the balance of direct and indirect pathways. When locomotor movement is in preparation, tonic activity of SNr neurons would continuously inhibit both systems. Once a trigger signal comes in, the direct pathway would release the activity of these systems, resulting in initiation of locomotion that is followed by smooth reduction of the level of muscle tone. Parallel organization from the SNr to the MLR/PPN would be therefore beneficial to regulate the level of muscle tone which accompanies with the initiation and termination of locomotion.

However particular emphasis has not placed on the importance of sustained inhibitory input from the SNr to SC during the period of saccade. Here we emphasize a crucial role of the sustained output from the basal ganglia to the target motor systems (for example, PPN and MLR) for controlling steady-state of ongoing movements such as

maintenance of postural muscle tone and rhythmic limb movements during locomotion. As previously described the sustained basal ganglia output signals may control the degree of freedom of the excitability of the target systems during movements. For example, when a subject needs to adapt heavy load during walking, the subject may unconsciously select an appropriate gait pattern which is associated with higher level of muscle tone and slower walking speed. Such a gait pattern could be realized by an increase in sustained SNr outputs to the PPN and the MLR, resulting in a decrease in the excitabilities of muscle tone inhibitory system and locomotor rhythm generating system. The sustained output from the basal ganglia may thus be necessary to automatically optimize the excitabilities of plural target motor systems so that the subject can unconsciously select an appropriate motor pattern.

4. BG-BS Systems for Brain Function in General.

Cognitive and psychotic processes have been observed in patients with degenerative disorders that involve primarily the basal ganglia such as Parkinson disease (Graybiel, 1995; Hikosaka et al., 2000; Mellers et al., 1995; Taylor et al., 1986) and Huntington's disease (McHugh and Folsten, 1975). In addition, awake-sleep states were also impaired in Parkinsonian patients (Bliwise et al., 2000; Eisensehr et al., 2001; Rye et al., 1999). In experimental studies in primates, limited lesions of the striatum induce deficits in rule acquisition (Divac 1972), cognition (Taylor et al., 1990), working memory performance (Goldman-Rakic, 1987) and selected attention (Batting et al., 1962). For example, Laplane et al. (1984) reported a patient with restricted bilateral pallidal lesions. He was appeared apathetic and unconcerned or attention deficits, and his affect was flattened and emotional responses were blunted in the absence of any motor disorder or akinesia (pure psychic akinesia). These symptoms were also described in progressive supranuclear palsy (PSP) in which major lesions were observed in the subcortical areas

including the PPN (Zweig et al., 1985). Because neuronal loss of cholinergic PPN neurons were observed not only in PSP (75-80%) but also Parkinson disease (43-57%) (Hirsch et al., 1987; Jellinger, 1988; Zweig et al., 1987, 1989), the loss of cholinergic PPN neurons in both diseases could attribute to attentive and cognitive impairments and sleep deficiencies in these diseases (Scarnati and Florio, 1997). These clinical evidences corroborate that the basal ganglia and their connections with the brainstem are also involved in the expression of non-motor function. In this section, we particularly discuss roles of the BG-BS system in the regulation of REM sleep, arousal state and an expression of emotional motor behaviors.

4-1; REM Sleep

The pontomesencephalic reticular formation has been known to comprise the ascending reticular activation system (ARAS; Moruzzi and Magoun, 1949), and the PPN is considered as a part of the ARAS (Garcia-Rill, 1997; Jones, 1991; Steriade, 1996). Cholinergic neurons in the PPN and laterodorsal tegmental nucleus are involved in not only the maintenance of arousal state but also generation of REM sleep (Datta, 2002; Koyama and Sakai, 2000; Maloney et al., 1999; Rye, 1997). Major ascending cholinergic projections into the non-specific thalamic nuclei provide desynchronization of electroencephalogram (EEG), i.e., EEG arousal (Steriade, 1996). Moreover, cholinergic projections to the lateral geniculate nucleus may provide ponto-geniculo-occipital (PGO) waves (McCormick and Bal, 1997; Steriade, 2001). Descending projections to the pontomedullary reticular formation (Lai et al., 1993; Shiromani et al., 1990) are involved in muscular atonia. Projections to the caudoventral pontine tegmentum are thought to be responsible for the generation of both REM and PGO waves (Vanni-Mercier and Debilly, 1998).

The SNr has a direct projection to the thalamic nuclei (Hendry et. al., 1979; Parent

et al., 1983) in addition to the PPN. Consequently, basal ganglia output may affect a REM sleep state by a modulation of the ARAS through dual systems (Fig.7A). One is through a direct nigrothalamic projection. The other is mediated via the PPN. We examined how the latter projection (GABAergic SNr-PPN projection) altered the activity of the REM generator and the muscle tone inhibitory system (Takakusaki et al., 2004b; Fig. 6B).

Stimulation of inhibitory region of the PPN induced REM which was associated with muscular atonia in decerebrate cats (REM with atonia; Fig. 6Ca). Conditioning stimulation applied to the lateral part of the SNr completely abolished the PPN-induced REM with atonia (Fig.6Cb). However, stimuli applied to the mid part of the SNr did not block REM but attenuated the muscular atonia, i.e., REM without atonia, which is relevant to REM sleep behavioral disorder (RBD; Culebras and Moore, 1989; Stanford, 1994), was induced by stimulation of the SNr (Fig.6Cc). These findings indicate that neuronal mechanisms for the induction of REM and muscular atonia are under the regulation of a GABAergic inhibition from the SNr. Patients with Parkinson's disease experience a number of sleep disorders, including reduction of REM sleep period and RBD (Bliwise et al., 2000; Eisensehr et al., 2001). Accordingly, our results may support the proposition that a decrease in dopaminergic activities in the basal ganglia is involved in the reduction of REM sleep and in RBD (Albin et al., 2000; Rye et al., 1999), and provide a rational explanation for pathogenesis of sleep disturbances in Parkinson disease.

However, the above idea does not agree with following findings. First, a group of nigrotegmental neurons increased their firing rate during REM sleep (Datta et al., 1991). Second, a c-*fos* expression of GABAergic SNr neurons during REM sleep was higher than during non-REM sleep and wakefulness (Maloney et al., 2002). These findings indicate that GABAergic SNr neurons do not necessarily contribute to the induction of REM sleep in normal condition. We consider that cholinergic-monoaminergic reciprocity (Hobson et

al., 1986) in the brainstem may play a more crucial role for the generation of REM sleep than the GABAergic SNr-PPN projection in normal state. However, the excessive GABAergic inhibition might affect the generation of REM sleep in Parkinsonian state.

4-2; Arousal, cognition and attention

A schema in Fig.6A also provides an important notion that a BG-BS system is involved in an arousal state or attention by modulating the activity of ARAS and the PPN. The PPN has cholinergic and non-cholinergic excitatory connections with dopaminergic neurons in the substantia nigra pars compacta (SNc) and other basal ganglia nuclei (Kitai, 1998; Takakusaki et al., 1996). These projections appear to play a role in more specific subcortical integration of motor and non-motor functions such as controlling behavioral arousal, attention and reward (Kitai, 1998). For example, an injection of muscimol into the PPN reduced the speed and amount of arm movements and delayed the onset of movements but the accuracy was rather maintained (Matsumura and Kojima, 2001). Moreover, Kojima et al. (1997) demonstrated that kainic acid-induced lesion in the unilateral PPN induced hemiparkisonism which was observed in the contralateral side of the injection. From these findings they suggest that the PPN may thus facilitate the voluntary limb movements through its excitatory connections with the dopaminergic neurons. Mesopontine dopaminergic neurons are also involved in the predictive reward which is specifically linked with reinforcement behaviors. Dopamine neurons are activated by rewarding events that are better than predicted, remain uninfluenced by events that are worse than predicted (Hikosaka et al., 2000; Schultz, 1998). Kobayashi et al. (2002) demonstrated that PPN neurons showed multi-modal activities during saccade tasks in alert monkey; their activities were related to the arousal levels, execution and preparation of movements, the level of task performance, and reward. They conclude that PPN may serve

as an integrative interface between the various signals required for performing purposive

behaviors (Kobayashi et al., 2004). We postulate that the PPN facilitates, possibly via

dopaminergic systems, the central processes for motor command generation and extrinsic

sensory processing by modulating arousal and attentive states.

Both neuroanatomical (von Krosigk et al., 1992; Nauta et al., 1978; Smith and

Bolam, 1990) and electrophysiological (Grace and Bunney, 1979; Hajos and Greenfield,

1994; Häusser and Yung, 1994; Saitoh et al., 2004; Paladini et al., 1999) studies

demonstrated that both dopaminergic neurons, as well as cholinergic neurons, receive

GABAergic inhibitory effects from the basal ganglia, particularly from the SNr.

Consequently a BG-BS system appears to involve the interdigitation of motor information

with information relating to reward and reinforcement by modulating the excitability of

both dopaminergic and cholinergic neurons.

4-3; Emotional expression

Stimulation of different areas in the basal forebrain can evoke different types of

goal directed behaviors (Grillner, 2003). An important component of these different

patterns of behavior is the locomotion that brings the animal to or away from a particular

location (Grillner et al., 1997). Following three types of locomotor systems that function in

different behavioral or motivational contexts are proposed (Sinnamon, 1993); an appetitive

system, a primary defensive system and an exploratory system. The nucleus accumbens

and the ventral pallidum, the older parts of the basal ganglia, are considered to take part in

locomotor control through the MLR (Mogenson et al. 1991; Slawinska and Kasicki, 1995).

Projections from the limbic structures (hippocampus and amygdala) to the nucleus

accumbens are possibly involved in the expression of emotional aspects of locomotor

behaviors (Grillner et al., 1997). Therefore, as shown in Fig.7, the mesopontine tegmentum

receives volitional signals from the cerebral cortex (volitional control) and emotional signals from the limbic structures (emotional control). Since the basal ganglia receive afferents from these two structures, a BG-BS system may play key roles for integration, selection or switching of volitionally-guided and emotionally-triggered motor behaviors (Fig.7).

In narcoleptic patients and animals, emotional signals elicit sudden loss of muscular tonus (cataplexy) (Nishino and Mignot, 1997). Thus emotional signals may have a capability of not only evoking locomotor behaviors but also eliciting muscular atonia. It has been shown that the orexinergic system contributes to maintain awake state (Saper et al., 2001; Taheri et al., 2002), and that deficiencies in the orexinergic system result in narcolepsy (Chemelli et al., 1999; Lin et al., 1999). Because the midbrain, including the SNr, the PPN and the MLR, receive orexinergic efferents from the perifornical lateral hypothalams (Nambu et al., 1999; Peyron et al., 1998), we propose that orexinergic projections to these midbrain areas must be critical for the expression of different aspects of emotional motor behaviors. Saper et al. (2001) have proposed that orexinergic projections to the midbrain are involved in switching sleep-awake states.

To test the above proposition, we examined effects of injections of orexin-A (60 μM-1.0 mM, 0.20-0.25 μl) into the MLR, PPN and the SNr upon motor behaviors in decerebrate cats (Takakusaki et al., 2004d). We observed that orexin injections into the MLR facilitated locomotion, while those into either the PPN or the SNr suppressed PPN-induced muscular atonia (cataplexic state). The latter effects were reversed by subsequent injection of bicuculline into the PPN. These findings suggest that the excitability seems to be higher in the locomotor system than in the atonia system in the presence of orexin. On the other hand, the excitability of the atonia system may be higher than that of the locomotor system in the absence of orexin. Thus emotional signals to the midbrain may induce locomotor behavior in the context of normal orexinergic system

function, but elicit cataplexy in narcolepsy when orexinergic system is disturbed. Therefore orexin may be a determinant of the selection of emotional motor behaviors (Takakusaki et al., 2003c).

An integration of "the locomotor system" and "the muscle tone control system" is essential to elicit a variety of locomotor patterns. The mesopontine tegmentum receives afferents from the cerebral cortex, the limbic systems, and hypothalamus, in addition to the basal ganglia. Thus the BG-BS system may contribute to the integrative process of volitional and emotional signals from these forebrain structures so that an animal can elicit appropriate locomotor behaviors depending on the behavioral context.

5；**Concluding Remarks**

We proposed that following roles can be played by the BG-BS system. First the system is involved in the automatic or unconscious control of movements that accompany voluntary movements. The basal ganglia outputs toward the brainstem and the thalamocortical loop may determine the degree of freedom of the automatic and volitional aspects of movements, respectively. Second, BG-BS systems may be involved in the maintenance of arousal and attentive states and in the regulation of REM sleep. These global brain function can be brought about by modulation of both cholinergic and dopaminergic systems arising from the brainstem. Third, the BG-BS systems may be involved in the appropriate expression of locomotor behaviors by integrating volitional and emotional signals from the forebrain structures. In this article, we presented several schemas in order to facilitate readers' interpretation. Obviously, these schemas are incomplete and overspecified. To test their validity, it must be necessary to formulate computational models based on the schemas and simulate the experimental results.

References

Albin, R.L., Koeppe, R.A., Chervin, R.D., Consens, F.B., Wernette, K., Frey, K.A., Aldrich, M.S., 2001. Decreased striatal dopaminergic innervation in REM sleep behavior disorder. Neurology 55, 1410–1412.

Alexander, G.E., Crutcher, M.D., 1990. Functional architecture of basal ganglia circuits: neural substrates of parallel processing. Trends Neurosci. 13, 267-271.

Amirali, A., Tsai, G., Schrader, N., Weisz, D., Sanders, I., 2001. Mapping of brain stem neuronal circuitry active during swallowing. Ann. Otol. Rhinol. Laryngol. 110, 502-513.

Anderson, M. Yoshida, M., 1980. Axonal branching patterns and location of nigrothalamic and nigrocollicular neurons in the cat. J. Neurophysiol. 43, 883-895.

Battig, K., Rosvold, H.E., Mishkin, M., 1962. Comparison of the effects of frontal and caudate lesions on discrimination learning in monkeys. J. Comp. Physiol. Psychol. 55, 458-463.

Beckstead, R.M., Domesick, V.B. Nauta, W.J.H., 1979. Efferent connections of the substantia nigra and ventral tegmental area in the rat. Brain Res. 175, 191-217.

Bliwise, D.L., Willians, M.L., Irbe, D., Ansari, F.P., Rye, D.B., 2000. Inter-rater reliability for identification of REM sleep in Parkinson's disease. Sleep 23, 671–676.

Brooks, D.J., 1995. The role of the basal ganglia in motor control: contributions from PET. J. Neurol. Sci. 128, 1-13.

Chase, M.H., Morales, F.R., 1990. The atonia and myoclonia of active (REM) sleep. Ann. Rev. Psychol. 41, 557–584.

Chase, M. H., Morales, F. R., Boxer, P., Fung S. J., Soja P. J., 1986. Effect of stimulation of the nucleus reticularis gigantocellularis on the membrane potential of cat lumbar motoneurons during sleep and wakefulness. Brain Res. 386, 237-244.

Chemelli, R.M., Willie, J.T., Sinton, C.M., Elmquist, J.K., Scammell, T., Lee, C., Richardson, J.A., Williams, S.C., Xiong, Y., Kisanuki, Y., Fitch, T.E., Nakazato, M., Hammer, R.E., Saper, C.B., Yanagisawa, M., 1999. Narcolepsy in orexin knockout mice: molecular genetics of sleep regulation. Cell 98, 437-451.

Chevalier, G., Deniau, J.M., 1990. Disinhibition as a basic process in the expression of striatal functions. Trends Neurosci. 13, 277-280.

Chevalier, G., Vacher, S., Deniau, J.M., Desban, M., 1985. Disinhibition as a basic process

in the expression of striatal functions. I. The striato-nigral influence on tect-spino/tecto-diencephalic neurons. Brain Res. 334, 215-226.

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

Datta, S., 2002. Evidence that REM sleep is controlled by the activation of brain stem pedunculopontine tegmental kainate receptor. J Neurophysiol. 87, 1790–1978.

Datta, S., Curró Dossi, R., Paré, D., Oakson, G., Steriade, M., 1991. Substantia nigra reticulata neurons during sleep-waking states: relation with ponto-geniculo-occipital waves. Brain Res. 566, 344-347.

Delong, M.R., 1990. Primate models of movement disorders of basal ganglia origin. Trends Neurosci. 13, 281–289.

Divac, I., 1972. Neostriatum and functions of the prefrontal cortex. Acta. Neurobiol. Exp. 32, 461-477.

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.

Dusterhoft, F., Hausler, U., Jurgens, U., 2000. On the search for the vocal pattern generator. A single-unit recording study. Neuroreport 11, 2031-2034.

Eisensehr, I., Lindeiner, H., Jager, M., Noachtar, S., 2001. REM sleep behavior disorder in sleep-disordered patients with versus without Parkinson's disease: is there a need for polysomnography? J. Neurol. Sci. 186, 7–11.

Fung, S.J., Barnes, C.D., 1981. Evidence of facilitatory coerulospinal action in lumbar motoneurons of cats. Brain Res. 261, 299-311.

Garcia-Rill, E., 1991. The pedunculopontine nucleus. Prog. Neurobiol. 36: 363- 389.

Garcia-Rill, E., 1997. Disorders of the reticular activating system. Med. Hypothesis 49, 379-387.

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

Goldman-Rakic, P.S., 1987. Circuitry of primate prefrontal cortex and regulation of behavior by representational memory. In: Plum F, Cowman M, (Eds.), Handbook of Physiology, the nervous system V. American Physiological Society, Bethesda, pp. 373-416.

Grace, A.A. and Bunney, B.S., 1979. Paradoxical GABA excitation of nigral dopaminergic

cells: indirect mediation through reticulata inhibitory neurons. Eur. J. Pharmacol. 59, 211-218.

Graybiel, A.M., 1995. Building action repertoires: memory and learning functions of the basal ganglia. Curr. Opin. Neurobiol. 5, 733-741.

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.

Grillner, S., Wallen, P., 2004. Innate versus learned movements--a false dichotomy? Prog Brain Res. 143, 3-12.

Grofova, I., Zhou, M., 1998. Nigral innervation of cholinergic and glutamatergic cells in the rat mesopontine tegmentum: Light and electron microscopic anterograde tracing and immunohistochemical studies. J. Comp. Neurol. 395, 359–379.

Habaguchi, T., Takakusaki, K., Saitoh, K., Sugimoto, J., Sakamoto, T., 2002. Medullary reticulospinal tract mediating the generalized motor inhibition in cats: II. Functional organization within the medullary reticular formation with respect to postsynaptic inhibition of forelimb and hindlimb motoneurons. Neuroscience 113, 65-77.

Hajos, M., Greenfield, S..A., 1994. Synaptic connections between pars compacta and pars reticulata neurones: electrophysiological evidence for functional modules within the substantia nigra. Brain Res., 660, 216-224.

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.

Häusser, M.A., Yung, W.H., 1994. Inhibitory synaptic potentials in guinea-pig substantia nigra dopamine neurones in vitro. J. Physiol. 479, 401-422.

Hendry, S.H.C., Jones, E.G., Graham, J., 1979. Thalamic relay nuclei for cerebellar and certain related fiber systems in the cat. J. Comp. Neurol. 185, 679-714.

Hikosaka, O., 1989. Role of basal ganglia in initiation of voluntary movements. In: M.A. Arbib and Amari, S (Eds.), Dynamic Interactions in Neural Networks: Models and

Data. Springer-Verlag, New York, pp. 153-167.

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.

Hikosaka O, Wurtz RH., 1983a. Visual and oculomotor functions of monkey substantia nigra pars reticulata. II. Visual responses related to fixation of gaze. J. Neurophysiol. 49, 1254-1267.

Hikosaka O, Wurtz RH., 1983b. Visual and oculomotor functions of monkey substantia nigra pars reticulata. III. Memory-contingent visual and saccade responses. J. Neurophysiol. 49, 1268-1284.

Hikosaka O, Wurtz RH., 1983c. Visual and oculomotor functions of monkey substantia nigra pars reticulata. IV. Relation of substantia nigra to superior colliculus. J. Neurophysiol. 49, 1285-1301.

Hirsch, E.C., Graybiel, A.M., Duyckaerts, C., Javoy-Agid, F., 1987. Neuronal loss in the pedunculopontine tegmental nucleus in Parkinson disease and in progressive supranuclear palsy. Proc. Natl. Acad. Sci. USA. 84, 5976-5980.

Hobson, J.A., Lydic, R., Baghdoyan, H.A., 1986. Evolving concepts of sleep cycle generation: from brain centers to neuronal populations. Behav. Brain Sci. 9, 371-448.

Honda, T., Semba, K., 1994. Serotoergic synaptic input to cholinergic neurons in the rat mesopontine tegmentum. Brain Res. 647, 299-306.

Hornykiewicz, O., Kish, S.J., Becker, L.E., Farley, I., Shannak, K., 1986. Brain neurotransmitters in dystonia musculorum deformans. N. Engl. J. Med. 315, 347-353.

Hutchins, K.D., Martino, A.M., Strick, P.L., 1988. Corticospinal projections from the medial wall of the hemisphere. Expl. Brain Res. 71, 667-672.

Inglis, W.L., Winn, P., 1995. The pedunculopontine tegmental nucleus: where the striatum meets the reticular formation. Prog. Neurobiol. 47, 1–29.

Isa, T., 2002. Intrinsic processing in the mammalian superior colliculus. Curr. Opin. Neurobiol. 12, 668-677.

Jellinger, K., 1988. The pedunculopontine nucleus in Parkinson's disease, progressive supranuclear palsy and Alzheimer's disease. J. Neurol. Neurosurg. Psychiatry. 51, 540-543.

Jones, B.E., 1991. Paradoxical sleep and its chemical/structural substrates in the brain. Neuroscience 40, 637–656.

Kitai, S.T., 1998. Afferent control of substantia nigra compacta dopamine neurons: anatomical perspective and role of glutamatergic and cholinergic inputs. Adv. Pharmacol. 42, 700-702.

Kobayashi Y, Inoue Y, Isa T., 2004. Pedunculopontine control of visually guided saccades. Prog. Brain Res., 143, 439-145.

Kobayashi, Y., Inoue, Y., Yamamoto, M., Isa, T., Aizawa, H., 2002. Contribution of pedunculopontine 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., Sakai, K., 2000. Modulation of presumed cholinergic mesopontine tegmental neurons by acetylcholine and monoamines applied iontophoretically in unanesthetized cats. Neuroscience 96, 723-733.

von Krosigk, M., Smith, Y., Bolam, J.P. & Smith, A.D., 1992. Synaptic organization of GABAergic inputs from the striatum and the globus pallidus onto neurons in the substantia nigra and retrorubral field which project to the medullary reticular formation. Neuroscience 50, 531-549.

Lai, Y.Y., Clements, J.R., Siegel, J.M., 1993. Glutamatergic and cholinergic projections to the pontine inhibitory area identified with horseradish peroxidase retrograde transport and immunohistochemistry. J. Comp. Neurol. 336, 321–330.

Lai, Y.Y., Siegel, J.M., 1988. Medullary regions mediating atonia. J. Neurosci. 8, 4790-4796.

Lai, Y.Y., Siegel, J.M., 1990. Muscle tone suppression and stepping produced by stimulation of midbrain and rostral pontine reticular formation. J. Neurosci. 10, 2727-2734.

Lai, Y.Y., Siegel, J.M. 1991. Pontomedullary glutamate receptors mediating locomotion and muscle tone suppression. J. Neurosci. 11, 2931-2937.

Laplane, D., Baulac, M., Widlocher, D., Dubois, B., 1984. Pure psychic akinesia with bilateral lesions of basal ganglia. J. Neurol. Neurosurg. Psychiatry. 47, 377-385.

Leonald, C.S., Llinás, R., 1994. Serotonergic and cholinergic inhibition of mesopontine

cholinergic neurons controlling REM sleep; an in vitro electrophysiological study. Neuroscience 59, 309-330.

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.

Magoun, M. W., Rhines, R., 1946. An inhibitory mechanism in the bulbar reticular formation. J. Neurophysiol. 9, 165-171.

Maloney, K.J., Mainville, L., Jones, B.E., 1999. Differential c-Fos expression cholinergic, monoaminergic and GABAergic cell groups of the pontomesencephalic tegmentum after paradoxical sleep deprivation and recovery. J. Neurosci. 19, 3057-3072.

Maloney, K.J., Mainville, L., Jones, B.E., 2002. c-Fos expression in dopaminergic and GABAergic neurons of the ventral mesencephalic tegmentum after paradoxical sleep deprivation and recovery. Eur. J. Neurosci. 15, 1-6.

Marsden, C.D., 1982. The mysterious motor function of the basal ganglia: The Robert Wartenberg Lecture. Neurology 32, 514-539.

Marsden, C.D., 1989. Slowness of movement in Parkinson's disease. Mov. Disord. 4 (suppl. 1), S26-37.

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

Matsumura, M., Kojima, J., 2001. The role of the pedunculopontine tegmental nucleus in experimental parkinsonism in primates. Stereotact. Funct. Neurosurg. 77: 108- 115.

Matsumura, M., Nambu, A., Yamaji, Y., Watanabe, K., Imai, H., Inase, M., Tokuno, H., Takada, M., 2000. Organization of somatic motor inputs from the frontal lobe to the pedunculopontine tegmental nucleus in the macaque monkey. Neuroscence 98, 97-110.

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

McCormick, D.A., Bal, T., 1997. Sleep and arousal: thalamocortical mechanisms. Ann. Rev. Neurosci. 20, 185-215.

McHugh, P.R., Folsten, M.F., 1975. Psychiatric syndromes of Huntington's chorea: a clinical and phenomenologic study. In: Beston F., Blumer D. (Eds.), Psychiatric aspects of neurological disease. vol. 13. Grune & Stratton, New York, pp. 267-286.

Mellers, J.D., Quinn, N.P., Ron, M.A., 1995. Psychotic and depressive symptoms in Parkinson's disease. A study of the growth hormone response to apomorphine. Br. J. Psychiatry 167, 522-526.

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., Kodama, T., Lai, Y.Y., Siegel, J.M., 2000. 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. 20, 8551-8558.

Mitani, A., Ito, K., Hallanger, A.E., Wainer, B.H., Kataoka, K., McCarley, R.W., 1988. Cholinergic projections from the laterodorsal and pedunculopontine tegmental nuclei to the pontine giganotocellular tegmental field in the cat. Brain Res. 451, 397–402.

Mogenson, G. I., 1991. The role of mesolimbic dopamine projections to the ventral striatum in response initiation. In: Shimamura, M., Griller, S., Edgerton, V.R. (Eds.), Neurobiological Basis of Human Locomotion, Japan Scientific Press, Tolyo, pp. 33-44.

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.

Moruzzi, G., Magoun, H.W., 1949. Brain stem reticular formation and activation of the EEG. Clin. Neurophysiol. 1, 455-473.

Murray M.P., Sepic S.B., Gardner G.M., Downs W.J., 1978. Walking patterns of men with parkinsonism. Am. J. Phys. Med. 57, 278-294.

Nambu, T., Sakurai, T., Mizukami, K., Hosoya, Y., Yanagisawa, M., Goto, K., 1999. Distribution of orexin neurons in the adult rat brain. Brain Res. 827, 243-260.

Nambu, A., Tokuno, H., Takada, M., 2002. Functional significance of the cortico-subthalamo-pallidal 'hyperdirect' pathway. Neurosci. Res. 43, 111-117.

Nauta, W.J., Smith, G.P., Faull, R.L., Domesick, V.B., 1978. Efferent connections and nigral afferents of the nucleus accumbens septi in the rat. Neuroscience 3, 385-401.

Nishino, S. and Mignot, E., 1997. Pharmacological aspects of human and canine narcolepsy. Prog. Neurobiol. 52, 27-78.

Obeso, J.A., Rodriguez, M.C., DeLong M.R., 1997. Basal Ganglia Pathophysiology, In: Obeso, J.A. DeLong, M.R., Ohye, C. and Marsden, C.D. (EDs.), The Basal Ganglia and New Surgical Approaches for Parkinson's Disease, Advance in Neurology, vol. 74, Lippincott-Raven Publishers, Philadelphia, pp.3-18.

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

Paladini, C.A., Celada, P. & Tepper, J.M. (1999) Striatal, pallidal, and pars reticulata evoked inhibition of nigrostriatal dopaminergic neurons is mediated by $GABA_A$ receptors in vivo. Neuroscience 89, 799-812.

Parent, A., Mackey, A., Smith, Y., Boucher, R., 1983. The output organization of the substantia nigra in primate as revealed by a retrograde double labeling method. Brain Res. Bull. 10, 529-537.

Pierrot-Deseilligny, C., Milea, D., Muri, R.M., 2004. Eye movement control by the cerebral cortex. Curr. Opin. Neurol. 17, 17-25.

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.

Rossignol S., 1996. Neural control of stereotypic limb movements. In: Rowell, L.B., Shepherd, J.T. (Eds.), Handbook of Physiology, sec. 12, Oxford University Press, New York, pp. 173-216.

Rye, D.B., 1997. Contributions of the pedunculopontine region to normal and altered REM sleep. Sleep 20, 757–788.

Rye, D.B., Johnston, L.H., Watts, R.L., Bliwise, D.L., 1999. Juvenile Parkinson's disease with REM sleep behavior disorder, sleepiness, and daytime REM onset. Neurology

53, 1868–70.

Saint-Cyr, J.A., Taylor, A.E., Nicholson, K., 1995. Behavior and the Basal Ganglia. In: Weiner, W.J. and Lang, A.E. (Eds.), Behavioral Neurology of Movement Disorders, Advance in Neurology, vol. 65. Raven Press, Ltd., New York, pp.1-28.

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.

Saitoh K, Isa T, Takakusaki K., 2004. Nigral GABAergic inhibition upon mesencephalic dopaminergic cell groups in rats. Eur. J. Neurosci. 19, 2399-2409

Sakai, M., Matsunaga, M., Kubota, A., Yamanishi, Y., Nishizawa, Y., 2000. Reduction in excessive muscle tone by selective depletion of serotonin in intercollicularly decerebrated rats. Brain Res. 860, 104-111.

Saper, C.B., Chou, T.C., Scammell, T.E., 2001. The sleep switch: hypothalamic control of sleep and wakefulness. Trends Neurosci. 24, 726-731.

Sato, M., Hikosaka, O., 2002. Role of primate substantia nigra pars reticulata in reward-oriented saccadic eye movement. J. Neurosci. 22, 2363-2373.

Scarnati, E., Florio, T., 1997. The pedunculopontine nucleus and related structures. Functional organization. Adv. Neurol. 74, 97-110.

Schultz, W., 1998. Predictive reward signals of dopamine neurons. J. Neurophysiol. 80, 1-27.

Scott, G., Westberg, K.G., Vrentzos, N., Kolta, A., Lund, J.P., 2003. Effect of lidocaine and NMDA injections into the medial pontobulbar reticular formation on mastication evoked by cortical stimulation in anaesthetized rabbits. Eur. J. Neurosci. 17, 2156-2162.

Semba, K. (1993) Aminergic and cholinergic afferents to REM sleep induction regions of the pontine reticular formation in the rat. J. Comp. Neurol. 330, 543-556

Shiromani, P.J., Lai, Y.Y., Siegel, J.M., 1990. Descending projections from the dorsolateral pontine tegmentum to the paramedian reticular nucleus of the caudal medulla in the cat. Brain Res. 517, 224–228.

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

Skinner, R.D., Kinjo, N., Ishikawa, Y., Biedermann, J.A., Garcia-Rill, E., 1990. Locomotor projections from the pedunculopontine nucleus to the medioventral medulla. Neuroreport 1, 207-210.

Slawinska, U., Kasicki, S., 1995. Theta-like rhythm in depth EEG activity of hypothalamic area during spontaneous or electrically-induced locomotion in the rat. Brain Res. 678,

117-126.

Smith, Y. and Bolam, J.P., 1990. The output neurones and the dopaminergic neurones of the substantia nigra receive a GABA-containing input from the globus pallidus in the rat. J. Comp. Neurol. 296, 47-64.

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.

Spann, B.M., Grofova, I., 1992. Cholinergic and non-cholinergic neurons in the rat pedunculopontine tegmental nucleus. Anat Embryol. 186, 215–227.

Sparks, D.L., 2002. The brainstem control of saccadic eye movements. Nature Rev. Neurosci. 3, 952-964.

Stanford, R.D., Morrison, A.D., Mann, G.L., Harris, J.S., Yoo, L., Ross, R.J., 1994. Sleep pattern and behaviour in cats with pontine lesions creating REM without atonia. J Sleep Res. 3, 233–240.

Steriade, M., 1996. Arousal: revisiting the reticular activating system. Science 272: 225-226.

Steriade, M., 2001. Impact of network activities on neuronal properties in corticothalamic systems. J. Neurophysiol. 86,1-39.

Taheri, S., Zeitzer, J.M. and Mignot, E., 2002. The role of hypocretins (orexins) in sleep regulation and narcolepsy. Ann. Rev. Neurosci. 25, 283-313.

Takakusaki K, Habaguchi T, Ohtinata-Sugimoto J, Saitoh K, Sakamoto T. 2003a. 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, Habaguchi T., Saitoh K, Kohyama, J., 2004c. 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., Kohyama, J., Matsuyama, K., 2003b. 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., 1993. Synaptic mechanisms acting on lumbar motoneurons during postural augmentation induced by serotonin injection into the rostral pontine reticular formation in decerebrate cats. Expl. Brain Res. 93, 471-482.

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, Ohinata-Sugimoto J, Saitoh K, Habaguchi T., 2004a. Role of basal ganglia-brainstem systems in the control of postural muscle tone and locomotion. Prog. Brain Res. 143, 231-237.

Takakusaki, K., Saitoh, K., Harada, H., Takahashi, K., Koyama, S., Okumura, T., 2003c. Is orexin a determinant of the selection of motor behaviors induced by emotional stimuli? Neurosci. Res. 46 (Suppl. 1), S-19.

Takakusaki, K., Saitoh, K., Harada, H., Okumura, T., Takahashi, K., Koyama, S.,2004d. Orexinergic projections to the midbrain mediate alternation of emotional behavioral states from locomotion to cataplexy. Soc. Neurosci., Abstr.

Takakusaki, K., Saitoh, K., Harada, H., Okumura, T., Sakamoto, T., 2004b. 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., 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., Shiroyama, T., Yamamoto, T., Kitai, S.T., 1996. Cholinergic and non-cholinergic tegmental pedunculopontine projection neurons in rats revealed by intracellular labeling. J. Comp. Neurol. 371, 345–361.

Taylor, J.R., Elsworth, J.D., Roth, R.H., Slodek, J.R., Redmond, D.E., 1990. Cognitive and motor deficits in the acquisition of an object retrieval/detour task in MPTP-treated monkeys. Brain 113, 617-637.

Taylor, J.R., Saint-Cyr, J.A., Lang, A.E., 1986. Frontal lobe dysfunction in Parkinson's disease. Brain 109, 845-883.

Turner, R.S., Anderson, M.E., 1997. Pallidal discharge related to the kinematics of reaching movements in two dimensions. J. Neurophysiol. 77, 1051-1074.

Van der Kamp, W., Berardelli, A., Rothwell, J.C., Thompson, P.D., Day, B.L., Marsden, C.D., 1989. Rapid elbow movements in patients with torsion dystonia. J. Neurol. Neurosurg. Psychiatry. 52, 1043-1049.

Vanni-Mercier, G., Debilly, G., 1998. A key role for the caudoventral pontine tegmentum in the simultaneous generation of eye saccades in bursts and associated ponto-geniculo-occipital waves during paradoxical sleep in the cat. Neuroscience 86, 571-85.

Wichmann, T., Delong M.R., 1996. Functional and pathological models of the basal

ganglia. Curr. Opin. Neurobiol. 6, 751-758.

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.

Zweig, R.M., Jankel, W.R., Hedreen, J.C., Mayeux, R., Price, D.L., 1989. The pedunculopontine nucleus in Parkinson's disease. Ann. Neurol. 26, 41-46.

Zweig, R.M., Whitehouse, P.J., Casanova, M.F., Walker, L.C., Jankel, W.R., Price, D.L., 1987. Loss of pedunculopontine neurons in progressive supranuclear palsy. Ann. Neurol. 22, 18-25.

Acknowledgments

Figure legends

Figure 1. Volitional and automatic control of locomotor movements
GABAergic basal ganglia output to the thalamocortical neurons and the brainstem neurons integrate volitional and automatic control processes of movements. See text for further explanation.

Figure 2. Effects of electrical and chemical stimulations of the mesopontine tegmentum
A. Experimental diagram. Either electrical or chemical stimulation was delivered to the lateral part of the mesopontine tegmentum. B. Effects on muscle activities following stimulation of the MLR (a) and the PPN (b). Each trace was obtained from the left (L) and right (R) soleus (Sol) muscles. A downward filled arrowhead in (a) indicates the onset of the treadmill. An open triangle in (b) indicates stimulation applied to the left pinna by pinching the scapha. C. (a) An injection of NMDA into the left MLR increased the bilateral muscle tone. (b) Commencement of the treadmill elicited locomotion. Downward and upward arrows indicate the onset and end of treadmill movements. (c) Two hours after the first injection, NMDA was injected into the left PPN and inhibited the bilateral soleus muscle activity. Pinching the pinna after 5 min (indicated by an open triangle) restored muscle activity. A dashed line above the recording indicates the period of the injection. D. Effective sites on coronal (a) and parasagittal (b) planes for evoking muscular atonia (filled circles) and locomotion (open circles). A shaded area in both planes indicates the PPN. E. Distribution of cholinergic neurons stained by choline acetyltransferase (ChAT) immunohistochemistry. Light microscopic photographs of coronal (a and b) and parasagittal (c and d) planes. Lower (a and c) and higher (b and d) magnification are shown in the right and left columns, respectively. Abbreviations; IC, inferior colliculus; CNF, cuneiform nucleus; SCP, superior cerebellar peduncle; PPN, pedunculopontine tegmental nucleus; NRPo, nucleus reticularis pontis oralis; RD, raphe dorsalis. Results in B-E are modified from Takakusaki et al. (2003a)

Figure 3.   Neural architecture of locomotion executing system (A) and the muscle tone inhibitory system (B). See text for explanation. Abbreviations: ACh, acetycholine; α, α-motoneuron; CPG, central pattern generator; E, extensor motoneurons, F, flexor motoneurons; FRA, flexion reflex afferents; GABA, γ-aminobutyric acid; LC, locus coeruleus; γ, γ-motoneuron; PMLS, pontomedullary locomotor strip; PRF, pontine reticular formation; RN, raphe nuclei; RSN, reticulospinal neuron; SLR, subthalamic locomotor region; SNr, substantia nigra pars reticulata; NRGc, the nucleus reticularis gigangocellularis.

Figure 4.   GABAergic nigrotegmental projections control locomotion and muscle tone. A. Experimental diagram. Either electrical or chemical stimulation was delivered to the SNr, the MLR and the PPN. B. (a) Quadrupedal locomotion observed at 15 min after injecting bicuculline into the MLR. (b) Another injection of bicuculline into the PPN in the same cat suppressed the locomotion. A dashed line above the recording indicates the period of the injection. Muscle activities were recorded from bilateral triceps brachial (TB) muscles and soleus muscles. C. Nigral control of postural muscle tone. The effects induced by the SNr (a) and PPN (b) on the postural muscle tone. PPN stimulation (20 μA) completely suppressed muscle tone. (c) When conditioning SNr stimuli of 50 μA were delivered, the PPN-effect was abolished. D. Nigral control of locomotion. (a) SNr stimulation did not change the level of muscle tone. (b) Locomotion on a moving treadmill belt induced by the MLR. (c) Conditioning SNr stimuli of 30 μA reduced step cycles, delayed the onset (indicated by open arrowhead) and disturbed rhythmic alteration of limb movements of MLR-activated locomotion. Results in B-D are modified from Takakusaki et al. (2003a)

Figure 5.   A hypothetical model for the control of movements by the basal ganglia A. GABAergic basal ganglia projections to the thalamocortical neurons may be involved in the volitional control aspects of movements, while those to the MLR and the PPN may be responsible for the automatic control processes of locomotor movements and postural muscle tone. B and C. See text for explanation. Abbreviations; BG, Basal ganglia; HD, Huntington's chorea; PD, Parkinson disease; PMRF, pontomedullary reticular formation.

Figure 6. Basal ganglia control of saccadic eye movements (modified from Hikosaka et al., 2003)

A. Neural structures involved in the basal ganglia control of saccadic eye movements. There are two parallel pathways, direct and indirect pathways, to the SNr. B. Firing patterns of CD, SNr and SC neurons during saccade. Disinhibition is a key mechanism for the initiation of saccade. C. Effects of indirect (a) and direct (b) pathways upon the SNr. The former enhance the inhibitory effects upon SNr neurons, while the latter inhibits SNr neurons. D. Two modes of basal ganglia action. The two pathways might work two ways. (a) Simultaneous mode. These two opposing effects should be superimposed in the SNr, yielding a sharper negative peak, resulting in more focusing the activity of target structures such as SC and thalamus. (b) The sequential mode. When a movement is in preparation, the indirect pathway would be continuously active so that the target of the basal ganglia is continuously inhibited in a non-selective manner. However, once a trigger signal comes in, the direct pathway would start working, and disinhibiting the target in a selective manner. Abbreviations: CD, caudate nucleus; D1, dopamine 1 receptor; D2, dopamine 2 receptor; GPe, external segment of globus pallidus; SC, superior colliculus; STN, subthalamic nucleus; SNc, substantia nigra pars compacta; SNr, substantia nigra pars reticulata.

Figure 7. Basal ganglia efferents to the PPN involved in the control of REM and muscular atonia.

A. Schematic model for the basal ganglia control of REM sleep. See text for detailed explanation. Briefly, the pontomesencephalic reticular formation including the PPN comprises ascending reticular activation system (ARAS). An interconnection between the mesopontine cholinergic nuclei and the caudoventral PRF could operate as a common generator of REM (Vanni-Mercier and Debilly, 1998). Descending projections from the PPN may activate REM generator and muscle tone inhibitory system in the PMRF to induce REM and muscular atonia. GABAergic basal ganglia efferents may affect REM sleep by modulating the activities of the PPN and the non-specific thalamic nuclei. B. Experimental diagram for examination of the involvement of a nigrotegmental projection in the control of REM and muscular atonia. C. (a) Stimulation of the PPN induced REM and muscular atonia. (b) Conditioning stimulation of the lateral part of the SNr diminished the PPN-effects. (c) Conditioning stimuli applied to the mid part of the SNr did not block

REM but blocked the muscular atonia (REM without atonia). Results in C are modified from Takakusaki et al. (2004b)

Figure 8. Possible neuronal mechanisms of integration of volitional, emotional and automatic control of motor behaviors. See text for explanation.
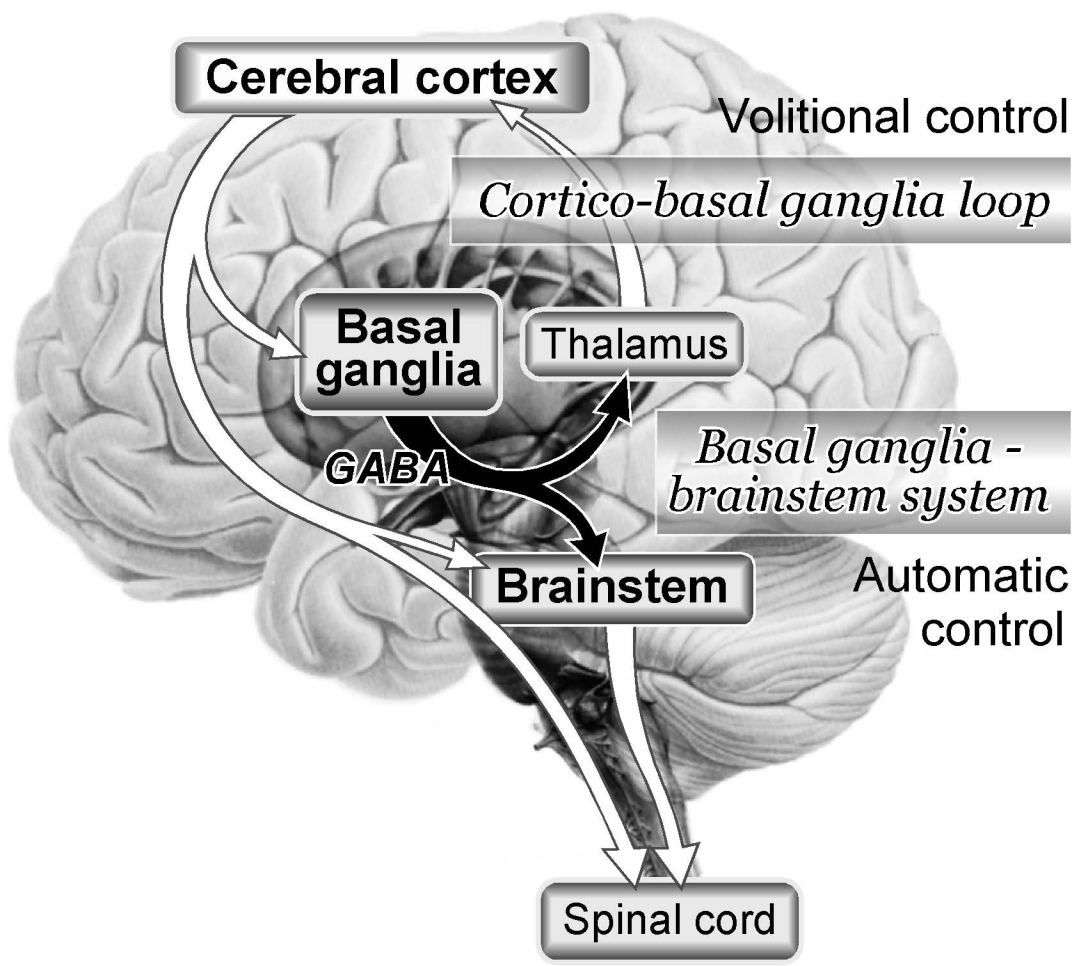
Cerebral cortex

Volitional control

Cortico-basal ganglia loop

Basal ganglia
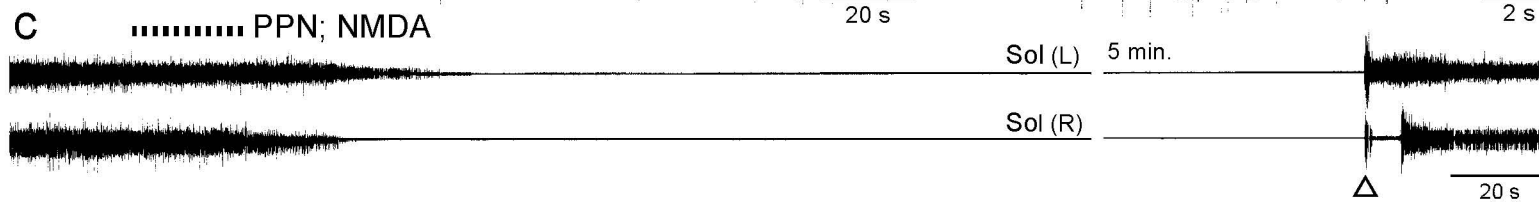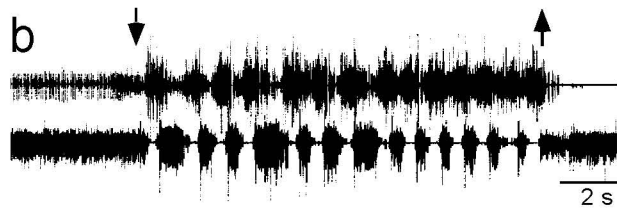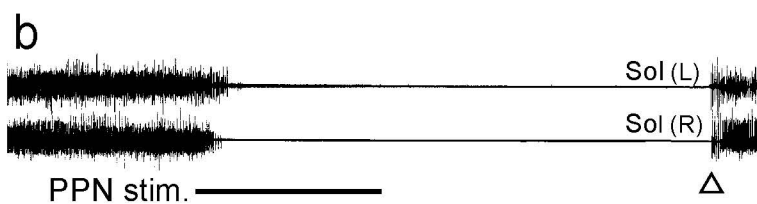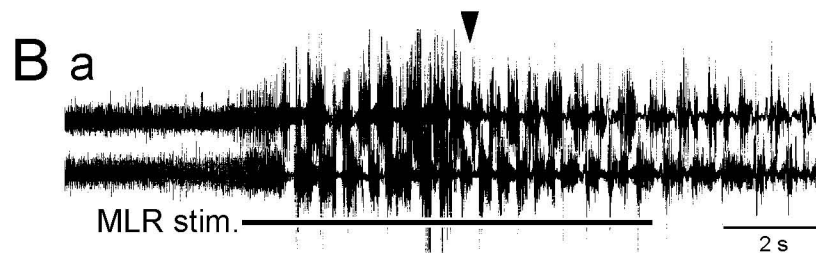
Thalamus

GABA

Basal ganglia - brainstem system
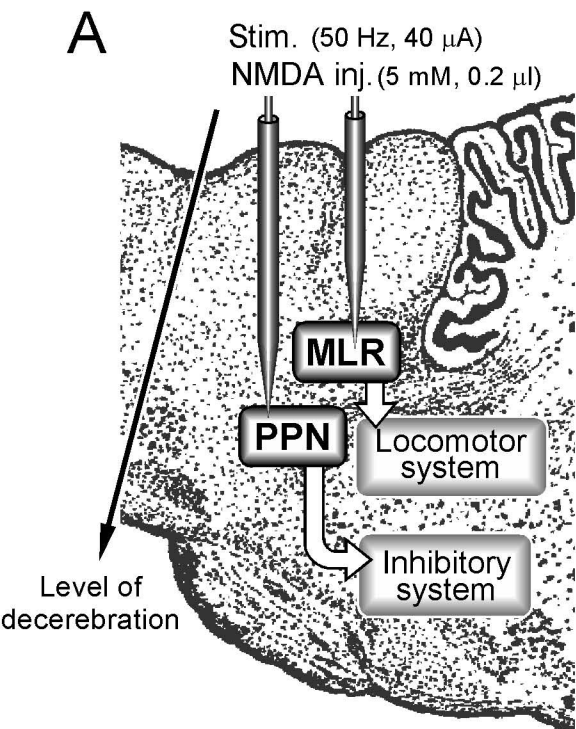
Brainstem

Automatic control

Spinal cord

A Stim. (50 Hz, 40 μA)
NMDA inj. (5 mM, 0.2 μl)

MLR

PPN

Locomotor system

Inhibitory system

Level of decerebration

D Stimulus sites

a
IC
RD
CNF
PPN
NRPo
P2

b
IC
CNF
PPN
SCP
LR4

E ChAT immunohistochemistry

a
CNF
PPN
P2
2.0 mm

b
CNF
PPN
SCP
P2
0.5 mm

c
CNF
SCP
PPN
L4
2.0 mm

d
PPN
SCP
L4
0.5 mm

B a
MLR stim.
2 s

b
Sol (L)
Sol (R)
PPN stim.
△

C a
MLR; NMDA

c
PPN; NMDA
20 s

b
Sol (L)
Sol (R)
5 min.
2 s
△
20 s

A

Basal ganglia

Locomotion executing system

Muscle tone facilitatory system

Rhythm generating system

Spinal cord

SLR

SNr

GABA

MLR

LC/RN

Excitatory

Inhibitory

Mixture

PMLS

Brainstem

Medullary RSN

Primary afferents

E

F

Muscles

CPG

Motoneurons

B

Basal ganglia

Muscle tone inhibitory system

SNr

GABA

PPN

ACh

LC/RN

Spinal cord

FRA

Primary afferents

Interneurons

PRF(NRPo)

Brainstem

Medullary RSN (NRGc)

Inhibitory interneuron

α

γ

Muscles

Motoneurons

A

Stim. Stim. Stim.
Bicuculline Bicuculline

MLR

PPN

SNr *GABA* NRPo
ACh

Bicuculline inj. (5 mM, 0.2 μl)
SNr stim. (30-50 μA, 100 Hz)
MLR stim. (20 μA, 50 Hz)
PPN stim. (20 μA, 50 Hz)

B

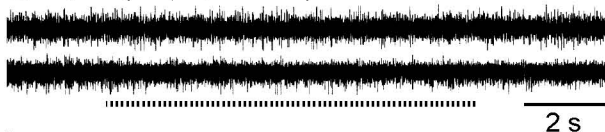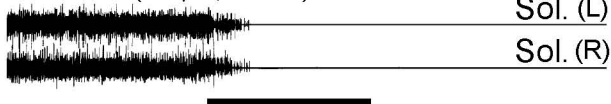**a** Bicuculline; MLR (5 mM, 0.2 μl)   **b** Bicuculline; PPN (5 mM, 0.2 μl)

TB. (L)
TB. (R)
Sol. (L)
Sol. (R)

10 s   10 s

C

a SNr (50 μA, 100 Hz)

2 s

b PPN (20 μA, 50 Hz)

Sol. (L)
Sol. (R)

c SNr (50 μA) + PPN (20 μA)

SNr
PPN

D

a SNr (50 μA, 100 Hz)

2 s

b MLR (20 μA, 50 Hz)

Sol. (L)
Sol. (R)

c SNr (30 μA) + MLR (20 μA)

Δ

SNr   MLR

A

Cerebral cortex

Volitional control

Basal ganglia

Thalamus

GABA

Automatic control

PPN   MLR

PMRF

Voluntary movements

Muscle tone, Locomotion

Spinal cord

B

decrease — Voluntary movements (amount / velocity) — *increase* — Cortex — BG

decrease — Locomotion (velocity) — *increase* — MLR — BG

Normal state

BG → PPN

decrease ← Muscle tone → *increase*

C

decrease — Voluntary movements (amount / velocity) — *increase* — Cortex — BG

decrease — Locomotion (velocity) — *increase* — MLR — BG

PD

a

HD   b

BG → PPN

decrease ← Muscle tone → *increase*

A

Cerebral cortex

Hyperdirect path.

Indirect path.

CD (−) (+)

D2 — D1

Direct path.

GPe

SNc
Dopamine

STN

SNr

SC

Saccadic eye movement

B

CD

SNr

Tonic inhibition   *Disinhibition*   *Tonic inhibition*

SC

Eye movements

C

a

Indirect path. (+)

CD

GPe (−)

STN (−)

SNr (+)

b

Direct path. (+)

CD

(−)

SNr

D

a Simultaneous ▪▪▪▶ Focusing

SNr

SC (−)

b Sequential ▪▪▪▶ Sequencing

SNr

SC (−)

Preparation

SNr

SC (−)

Execution

A

EEG desynchronization

Cerebral cortex

Basal ganglia

Thalamus

GABA

ARAS

PPN

REM generator

RF

Rapid eye movements

Inhibitory system

Muscular atonia

Spinal cord

B

Stim. (60 µA, 100 Hz)

Stim. (40 µA, 50 Hz)

SNr → **PPN** → Inhibitory system

→ REM generator

C

a

EOG
Sol. (L)
Sol. (R)

PPN

5 s

b

Lateral SNr

PPN

c

Mid SNr

PPN

Cerebral cortex

Volitional control

Cortico-basal ganglia loop

Basal ganglia

Thalamus

GABA

Basal ganglia - brainstem system

Limbic structures

Brainstem

Automatic control

Limbic - brainstem system

Emotional control

Spinal cord