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☐ Review Article ☐

The Pedunculopontine Nucleus: Its Role in the Genesis of Movement Disorders

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Abstract

The pedunculopontine nucleus (PPN) is located in the dorso-lateral part of the ponto-mesencephalic tegmentum. The PPN is composed of two groups of neurons: one containing acetylcholine, and the other containing non-cholinergic neurotransmitters (GABA, glutamate). The PPN is connected reciprocally with the limbic system, the basal ganglia nuclei (globus pallidus, substantia nigra, subthalamic nucleus), and the brainstem reticular formation. The caudally directed corticolimbic-ventral striatal-ventral pallidal-PPN-pontomedullary reticular nuclei-spinal cord pathway seems to be involved in the initiation, acceleration, deceleration, and termination of locomotion. This pathway is under the control of the deep cerebellar and basal ganglia nuclei at the level of the PPN, particularly via potent inputs from the medial globus pallidus, substantia nigra pars reticulata and subthalamic nucleus. The PPN sends profuse ascending cholinergic efferent fibers to almost all the thalamic nuclei, to mediate phasic events in rapid-eye-movement sleep. Experimental evidence suggests that the PPN, along with other brain stem nuclei, is also involved in anti-nociception and startle reactions. In idiopathic Parkinson's disease (IPD) and parkinson plus syndrome, overactive pallidal and nigral inhibitory inputs to the PPN may cause sequential occurrences of PPN hypofunction, decreased excitatory PPN input to the substantia nigra, and aggravation of striatal dopamine deficiency. In addition, neuronal loss in the PPN itself may cause dopamine-resistant parkinsonian deficits, including gait disorders, postural instability and sleep disturbances. In patients with IPD, such deficits may improve after posteroventral pallidotomy, but not after thalamotomy. One of the possible explanations for such differences is that dopamine-resistant parkinsonian deficits are mediated to the PPN by the descending pallido-PPN inhibitory fibers, which leave the pallido-thalamic pathways before they reach the thalamic targets.

Key Words: Pedunculopontine nucleus, idiopathic Parkinson's disease, progressive supranuclear palsy

INTRODUCTION

In spite of great progress recently in our knowledge about the basal ganglia, the mechanisms responsible for many movement disorders are not yet fully understood. Some parkinsonian deficits, including disorders of gait, postural instability, freezing, unexplained falls, sleep disturbances, and sensory symptoms, tend to be resistant to levodopa therapy, and can not be explained merely by dysfunction of the nigrostriatal dopaminergic pathway.[1-4] Such dopamine-resistant parkinsonian deficits are more frequent in patients with parkinson-plus syndromes, where more wide-spread degenerative brain stem lesions occur.[5,6]

The effects of pallidotomy on parkinsonian deficits also highlight the role of descending basal ganglia influences on brainstem structures. In patients with idiopathic Parkinson's disease (IPD), thalamotomy is effective mainly for tremor and rigidity.[7] On the other hand, a posteroventral pallidotomy improves most parkinsonian symptoms, including akinesia, disorders of gait, postural instability, falls, and sleep disturbances, as well as tremor and rigidity.[8] To explain such discrepancies in the outcome of treatment, the traditional concept of the nigro-striato-pallido-thalamocortical neuronal circuits controlling voluntary movements may need to be extended to include the influence of the descending nigro-striato-pallidal pathways on the brain stem nuclei.[9]

The pedunculopontine nucleus (PPN) is connected

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with many other brainstem neuronal structures. However, the PPN differs from other brainstem reticular nuclei because of its reciprocal connections with the basal ganglia nuclei. The PPN is the most caudally located neuronal structure which has direct connection with the basal ganglia.[10,11] The neuronal connections of the PPN and the results of experimental studies in animals suggest its involvement in a number of parkinsonian deficits and other neurological deficits.

ANATOMY OF THE PPN

The PPN is a columnar shaped neuronal cluster, lying in the dorsolateral part of the ponto-mesencephalic tegmentum, and its main mass is located at the level of the trochlear nucleus just above the ponto-mesencephalic junction.[12] In humans and other primates, large neurons with hyperchromatic nuclei make the PPN more or less distinctive from the surrounding brain stem nuclei. The retrorubral field separates the rostral end of the PPN from the substantia nigra (SN). The PPN extends caudally to the area rostral to the pontine parabrachial nuclei; it is bounded medially by the superior cerebellar peduncle, laterally and ventrally by the medial lemniscus, and dorsally by the nucleus cuneiformis.[10,13]

The PPN consists of morphologically and neurochemically heterogeneous groups of neurons. Olszewski and Baxter[13] divided the human PPN into two subnuclei on the basis of the size and density of the neurons. The pars compacta (PPNc) is a prominent and compact cluster of large neurons; pars dissipatus (PPNd) is composed of small or medium-sized neurons scattered within the superior cerebellar peduncle and central tegmental tract, with uncertain boundaries. The PPNc is smaller, and can be seen only in the dorsolateral part of the caudal half of the PPN, whereas the PPNd forms the principal area of the PPN and is present throughout its rostrocaudal axis.

Choline acetyl-transferase (ChAT) staining labels a continuous band of large neurons (diameter $>20\,\mu m$) in the ponto-mesencephalic reticular formation. These cholinergic neurons have been named the Ch5 and Ch6 sectors. Most Ch5 neurons are within the territory of the PPN, and the majority of Ch6 neurons are within the area corresponding to the lateral dorsal tegmental nucleus (LDTg).[14,15] The distribution of NADPH-diaphorase positive neurons is similar to that of the ChAT-positive neurons.[16] About 80-90 % of the large cholinergic neurons in these areas also contain substance P.[17]

In rats, several studies, using anterograde and retrograde axonal tracing techniques or ChAT immunohistochemical methods, have consistently shown two clusters of PPN neurons with clear boundaries. The non-cholinergic neurons are located in the area medial to the cholinergic neurons. These small to medium-sized neurons are reciprocally connected with the basal ganglia, whereas the large cholinergic neurons send efferent fibers to the thalamus. Some authors have therefore argued that the term 'PPN' should be limited to the cholinergic neuronal cluster, while the non-cholinergic neuronal cluster should be separately termed 'the midbrain extrapyramidal area'.[18-21] However, many other cases of evidence have been reported contradicting a clear boundary between the subnuclei of the PPN.[10,12,15,16,22-29] PPN neurons, therefore, appear to have some preferential neuronal connections according to their location, size, and cytochemical characteristics, but the boundaries of the subnuclei do not seem to be very clear. In this review, we use the term 'PPN' to refer to the area in the dorsal ponto-mesencephalic tegmentum as defined by Olszewski and Baxter.[13]

NEURONAL CONNECTIONS OF PPN (Fig. 1)

Because of its long rostrocaudal axis and ventrolateral shift, the PPN contacts many other brainstem neuronal structures, including the retrorubral nucleus, cuneiform nucleus and parabrachial nucleus. PPN neurons also give rise to long dendrites radiating in many directions to receive inputs from the surrounding neuronal pathways, including the medial, lateral, central and dorsal tegmental bundles, medial longitudinal fasciculus, spinothalamic tract, and superior cerebellar peduncle.[19]

The rostrally and caudally projecting fibers of the PPN largely originate from different cells, and less than 5 % of PPN neurons send efferent fibers in both directions. Rostrally projecting PPN neurons outnumber caudally projecting neurons by 5.4 to 1.[10]

The PPN is connected to other neuronal structures mainly by five pathways: (1) dorsal ascending fibers

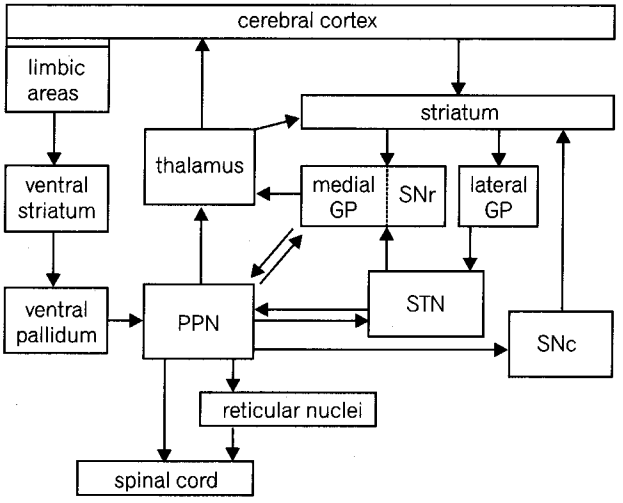

Fig. 1. Schematic diagram of major efferent and afferent neuronal connections of the pedunculopontine nucleus. Arrowheads indicate the direction of neuronal connections. Abbreviations: GP, globus pallidus; PPN, pedunculopontine nucleus; SNc, substantia nigra pars compacta; SNr, substantia nigra pars reticulata; STN, subthalamic nucleus.

(mainly cholinergic), within the dorsal tegmental pathways, project to nearly all the thalamic nuclei; (2) ventral ascending fibers (mainly non-cholinergic) connect the PPN to the GP, STN, SN and ventral tegmental area; (3) one group of fibers connects the PPN to the surrounding brainstem nuclei; (4) one group of descending fibers projects bilaterally to the medullary and pontine reticular formation including nucleus raphe magnus, nucleus pontis oralis and nucleus pontis caudalis; and (5) there are also sparse bilateral direct spinal projections.[10,30-32]

Neuronal connections of the PPN with the cerebral cortex

The PPN is connected reciprocally with the ipsilateral prefrontal and motor cortex.[32-34] The cortico-tegmental tract, intermingled with the pyramidal tract, descends until the level caudal to the SN, where the fibers leave the cerebral peduncle and pass dorsally to terminate in the PPN.[31]

Neuronal connections of the PPN with the limbic-ventral striatal-ventral pallidal system

The limbic areas, including the amygdala, hippocampus and cingulate gyrus, send efferent fibers to the nucleus accumbens.[35] The nucleus accumbens also receives dopaminergic afferent input from the midbrain ventral tegmental area.[36] The nucleus accumbens sends GABA-ergic projections to the ventral pallidum (substantia innominata and lateral preoptic area).[14] The ventral pallidum sends efferent fibers to the PPN.[37]

Neuronal connections of the PPN with the thalamus

More than 60% of PPN cholinergic neurons send efferent fibers to the thalamus through dorsal ascending tegmental pathways. These fibers comprise about 90% of the tegmento-thalamic cholinergic projections.[18,22] The majority of the cholinergic inputs to the medial geniculate, dorsolateral geniculate, centrolateral, dorsolateral, ventral anterior (VA), and ventrolateral (VL) thalamic nuclei arise from the PPN, as do one third of cholinergic inputs to the anteroventral, ventromedial, dorsomedial, and intralaminar thalamic reticular nuclei originate from the PPN. The PPN also sends efferent fibers to the centromedian and parafascicular thalamic nuclei, which give rise to thalmo-striatal fibers.[20,38] Some PPN efferent fibers cross the midline through the posterior commissure or thalamic mid-line nuclei to reach the contralateral thalamus.[12,18,39] Retrograde tracing with horseradish peroxidase (HRP) injection into PPN labelled only a few thalamic neurons in the lateral geniculate body and reticular nucleus.[21]

Neuronal connections of the PPN with the basal ganglia

Globus pallidus-PPN: The medial segment of the globus pallidus (GPm) sends efferent fibers to four major targets: the VA/VL thalamic nuclei, centromedian thalamic nucleus, lateral habenula and PPN.[40] GABA-ergic GPm neurons send inhibitory efferent fibers mainly to the ipsilateral PPN, but 10−20% pass to the contralateral PPN.[41-44]

About 80% of the pallidal efferent fibers to the PPN send collateral fibers to the VA/VL thalamic nuclei.[42,45] The pallido-PPN fibers follow the pallido-thalamic pathways, until they leave at the level of Forel's field H. Subsequently, they divide into medial and lateral descending pathways. The medial descending pathway passes dorsomedially to join the medial longitudinal fasciculus in the prerubral field, and

terminates in the PPN. The lateral pathway descends in the ventrolateral tegmentum between the SN and red nucleus. These fibers are intermingled with fibers in the medial lemniscus. At the level of the caudal midbrain, they pass dorsally to terminate in the PPN.[46-48]

In monkeys, retrograde axonal tracing studies showed that the GPm sends efferent fibers to the PPN, but to a wider area of PPN than do the entopeduncular nuclei in rodents.[11,42] Autoradiographic studies have confirmed such phylogenetic differences; in rats, the PPN receives most of its afferents from the SN,[21,31] in the monkey, the PPN receives its most extensive afferents from the GPm.[11,42,47] In cats, less than 10% of neurons in the entopeduncular nucleus are activated by antidromic electrical stimulation of the PPN,[40,49] but in the monkey, 94% of GPm neurons are so activated.[45]

In rats, electrical stimulation of the PPN increases the firing rates of neurons in the entopeduncular nucleus.[50] In the monkey, PPN-efferent fibers to the subthalamic nucleus (STN) and SN are much more massive than those to the pallidal complex.[47,51]

Substantia nigra-PPN: Diffusely organized descending fibers (largely non-dopaminergic) leave the SN, mainly originating from the lateral two-thirds of the substantia nigra pars compacta (SNc) and caudal part of the substantia nigra pars reticulata (SNr).[21,31] At the lateral corner of the central grey substance, this bundle divides into two branches at a right angle. The nigro-tectal fibers pass dorsolaterally to terminate in the deeper layer of the colliculus. A smaller descending bundle passes to the area behind the trochlear nucleus, and terminates mainly in the PPN.[52] These nigral fibers are also connected to the medullary reticular formation and the VA/VL thalamic nuclei.[42,53]

Antidromic electrical stimulation of the PPN activates less than 10% of the SN neurons.[49,54] However, these GABA-ergic afferent endings from the SN make profuse synaptic contacts with the cell bodies and dendrites of PPN neurons.[55,56] Intracellular monitoring after electrical stimulation of the SN shows inhibitory postsynaptic potentials in both cholinergic and non-cholinergic PPN neurons.[32,56,57] On the other hand, striatal stimulation results in disinhibition of PPN neurons, by causing inhibition of SN neurons.[58]

PPN neurons send monosynaptic efferent fibers mainly to the ipsilateral SNc, but there are a few efferent fibers to the SNr, which receives its main excitatory input from the STN.[23,42,56,59,60] In rats, antidromic electrical stimulation of SN neurons activates about 18% of the PPN neurons.[61] Orthodromic electrical stimulation of the PPN activates 16% of SN neurons after a short latency, possibly via a monosynaptic link, and 22% after a longer latency.[49] Such excitation is reduced markedly by a lesion placed at the STN. These findings suggest the existence of dual PPN pathways to the SN (direct monosynaptic connection and indirect connection via the STN).[54]

About 50% of excitatory PPN efferent fibers to the SNc contain glutamate.[62-65] The STN also sends glutamatergic efferents to the SNc. The glutamatergic effects from the PPN are mediated by AMPA (A-amino-3-hydroxyl-5-methyl-4-isoxazolepropionate) receptors, and the subthalamic inputs by NMDA (*N*-methyl-*D*-aspartate) receptors.[66]

In the rat and ferret, a double immunohistochemical study using antibodies to ChAT and tyrosine hydroxylase demonstrated multiple asymmetric cholinergic terminals on the dendrites of SN dopaminergic neurons.[25] Nigrostriatal neurons have nicotinic receptors. Acetylcholine or cholinergic agonist applied iontophoretically to the SN increases both the firing rates of nigral dopaminergic neurons, and striatal extracellular dopamine concentration.[27,67,68]

In a study using in-vitro slice preparation of the rat brain, PPN stimulation induced monosynaptic excitatory postsynaptic potentials (EPSPs) in the SNc dopaminergic neurons. The EPSPs were partially suppressed by the application of antiglutamatergic agents to the SN. The EPSPs resistant to antiglutamatergics were almost completely eliminated by the application of anticholinergics.[69]

Subthalamic nucleus-PPN: The subthalamic efferent fibers to the ponto-mesencephalic tegmental area are difficult to identify.[42] However, at least 1% of STN neurons (about 100 cells), mainly located in the lateral strip of the STN, send efferent fibers to the lateral part of the ipsilateral PPN.[31,70,71] Retrograde double axonal tracing technique, with injection of two different dyes into the GP and SN, revealed that more than 94% of single STN neurons send axon collaterals both to the GP and SN.[72] The STN efferent fibers to the striatum are mainly collaterals of the STN efferent fibers to the GP and

SN, whereas STN projections to the PPN are very rarely collaterals of these.[70,73]

Anterograde[51] and retrograde[59,71] labeling studies demonstrated profuse projections from the PPN to the bilateral STN. Orthodromic electrical stimulation of the PPN activates some STN neurons that send efferent fibers to the GP or SN. Some of the PPN terminals in the STN are collaterals of the PPN efferent fibers to the GP.[71]

Striatum-PPN: The PPN sends efferent fibers sparsely o the bilateral striatum, but predominantly to the ipsilateral side. The axon terminals in the striatum are poorly arborized. Little is known about the electrical and chemical characteristics of PPN efferent fibers to the striatum.[51,74]

Neuronal connections of the PPN with the brainstem nuclei and cerebellum

The brainstem reticular nuclei and midbrain periaqueductal gray matter are the major brainstem structures connected with the PPN. Other significant but less prominent structures include the superior colliculus, oculomotor nucleus, cuneiform nucleus, parabrachial nucleus, dorsal raphe nucleus, sensory nuclei, and cerebellum and related neuronal structures.

Reticular nucleus-PPN: The PPN receives more dense afferent fibers from the pontine reticular formation than from the medullary reticular formation.[21] The main caudally-directed cholinergic and non-cholinergic PPN efferent fibers terminate bilaterally in the pontine reticular nuclei oralis and caudalis and in the ventromedial portion of the gigantocellular reticular nucleus.[10,32,56,59,75]

Other brainstem nuclei-PPN: Retrograde labelling studies show that the intermediate layers of the superior colliculus, which receives afferent fibers from the SNr, send efferent fibers to the PPN. The lateral and ventrolateral parts of the periaqueductal gray matter also send dense efferent fibers to the PPN.[21]

Cholinergic dorsal ascending fibers originating from the PPN pass through the pretectum as a part of the dorsal tegmental pathways. Some fibers leave the main bundle, and then turn medially to terminate in the central tegmental gray, superior and inferior colliculi, and pretectal nucleus. The PPN also sends efferent fibers to the accessory oculomotor nuclei in the midbrain, and to eye-movement-related structures in the lower brainstem.[32]

Cerebellum and red nucleus-PPN: In monkeys, efferent fibers from the deep cerebellar nuclei send collateral fibers to the entire rostro-caudal extent of the PPN before they reach their thalamic targets.[76] In rats, a retrograde tracing study injecting HRP into the PPN also labeled many neurons in the dentate and interpositus nuclei of the cerebellum, via axons in the superior cerebellar peduncle.[21] Major cholinergic afferents to the fastigial nucleus of the cerebellum originate from the PPN.[77]

Neuronal connections of the PPN with the spinal cord

In the rat, injection of retrograde tracer into the PPN labeled neurons in the cervical, thoracic and lumbar dorsal horns.[32] Bilateral injections of HRP into the cervical cord, lumbar enlargement, or sacral cord labeled a moderate number of non-cholinergic PPN neurons. These projecting neurons are mainly located in the medial half of the PPN (PPNd), to which the basal ganglia afferent fibers are also connected.[10]

PHYSIOLOGY OF PPN

In terms of electrophysiological characteristics, PPN neurons can be divided into three groups. The first group of neurons does not fire spontaneously, and is characterized by low-threshold calcium spikes following hyperpolarization. Such rebound excitation may cause bursting activities. The second group of neurons also does not fire spontaneously, and displays low threshold spikes. However, they are characterized by a transient outward current, which delays the return to the baseline after hyperpolarization, accounting for the lack of rebound activation. These two groups of neurons may exhibit bursting patterns of neuronal firing. The third group of neurons exhibits outward conductance, like as the second group of neurons, but does not exhibit a low-threshold spike. They show delayed return to the baseline after hyperpolarization, and slow repetitive tonic firing. Non-cholinergic PPN neurons have characteristics suitable for phasic firing, and cholinergic neurons for tonic firing.[78,79]

Takakusaki et al. classified PPN neurons into two

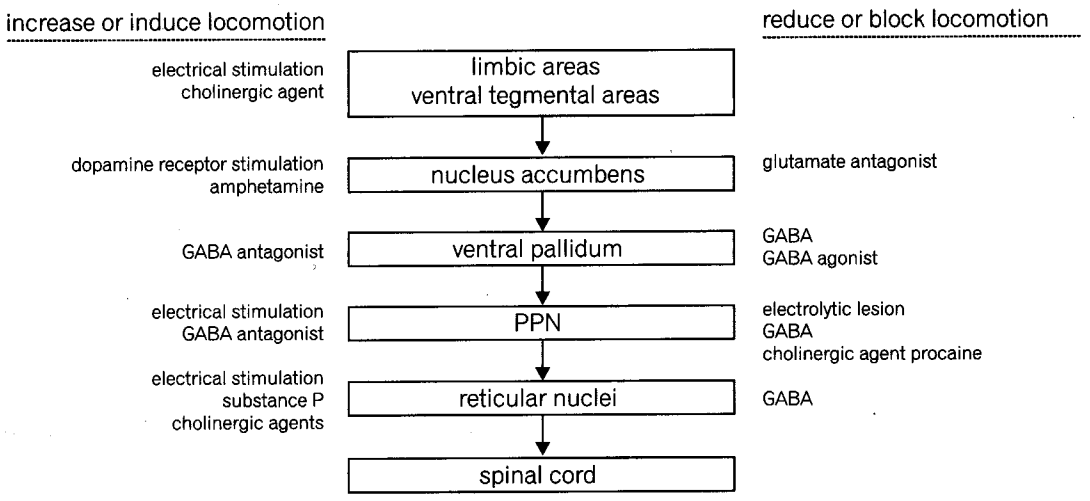

Fig. 2. Schematic diagram shows neuronal structures involved in the genesis of locomotion and variable factors that could induce or reduce locomotor activities.

types. Their type I neurons display low-threshold calcium spikes following hyperpolarization, whereas type II neurons exhibit a transient outward current.[80-82] They divided type II neurons into short and long spike-duration neurons. Short-duration neurons have higher firing rates and greater excitability. They seem to be involved in phasic neuronal processes. In contrast, long-duration neurons show more stable and rhythmic firing, and are adapted to the maintenance of steady-state rhythmic activities. Both groups of neurons may be associated with behavior control (arousal and sleep), and with motor control related to the basal ganglia.

Locomotion

The concept of a mesencephalic locomotor region (Fig. 1 and 2): In cats with precollicular-premammillary transection, spontaneous locomotion occurs. Such animals show rhythmic activities within the dorsolateral midbrain tegmental area, correlating with electromyographic activities of the limb muscles. These persist even after restraint of the limbs to remove peripheral afferent inputs.[83-85]

In cats with precollicular-postmamimally transection, stimulation of the midbrain tegmental area is required to induce locomotion on a treadmill.[83,86,87] As the strength of current is increased, the frequency of the step cycle changes to a rapid walk, and then to a gallop.[86,88] In contrast, electrolytic lesions of the dorsolateral midbrain area prevent induced locomotion.[87]

The midbrain tegmental area which induces locomotor activities under stimulation has been called the 'mesencephalic locomotor region' (MLR). Because the MLR has been defined on the basis of electric stimulation, there has been controversy over the anatomical boundaries of the MLR. Nevertheless, many experimental studies have demonstrated that it includes brain areas corresponding to the PPN and cuneiform nucleus.[39,49,79,87,88]

Locomotion induced by electric stimulation could be a result of the activation of neurons within the MLR or of neuronal pathways passing nearby. However, in cats with precollicular-postmammillary transection, GABA antagonist injection into the MLR induces a pattern of locomotion similar to that following electrical stimulation, suggesting a neuronal origin of the induced locomotion.[89]

The medial ventral medullary region shares common characteristics with the MLR. Single-unit recording from medullary neurons showed that 31% of cells exhibit rhythmic activities related to electromyography (EMG) activities, 34% exhibit periodicity, but have no correlation with EMG activities, and 35% were tonic firing neurons. Of the EMG-related neurons, 27% were associated with flexor muscle activity, and 63% with extensor muscle activity.[90] Low-amplitude (less than 70 μA) electrical stimulation of the medial ventral medullary areas induces

episodes of locomotion in cats with precollicular-postmammillary transection. Injection of substance P or cholinergic agents into these areas also induces locomotion. In contrast, GABA injection into these areas blocks locomotion induced either by electrical or chemical stimulation of the medioventral medulla, or by MLR stimulation.[91,92]

However, the pattern of locomotion induced by medullary stimulation differs from that following MLR stimulation. Medullary stimulation is more frequently associated with the amount of muscle activity, but not with the timing of its beginning or ending.[93,94] The duration of locomotion following medullary chemical stimulation is shorter. In contrast to the hindlimb movements which occur following MLR stimulation, the primary responses of medullary stimulation are mainly confined to the forelimbs.[91,92] These reticular medullary areas therefore do not appear to be the origin of locomotor activities, but seem to act as an interface connecting MLR activities to the spinal cord.[95]

Initiation, acceleration, deceleration, and termination of walking, running, or swimming seem to be regulated by the MLR. In addition to such rhythmic locomotor activity, the MLR may also provide appropriate postural tone for locomotion, righting reflex, and protective reaction, through connections with the reticulospinal, tectospinal and vestibulospinal tracts.[96,97] All these activities are modulated by inputs from the cerebral cortex, limbic system, basal ganglia, brain stem nuclei, cerebellum, and peripheral proprioceptive feedbacks.[86,88,94,98-100]

Initiation of locomotion (Fig. 2): Locomotion can be induced by carbachol (muscarinic cholinergic agent) injection into the bilateral hippocampus.[101] Stimulation of dopaminergic receptors in the nucleus accumbens also induces locomotion.[37,102] Disinhibition of the pallidum produced by picrotoxin (GABA antagonist) injection induces locomotor activities. In test animals, the c-Fos immunoreactive neurons count in the ipsilateral PPN increased 3.5 times compared to that of control animals, suggesting a hyperactive condition of the PPN neurons.[103] On the other hand, induced locomotion is blocked by injection of glutamate antagonist into the nucleus accumbens[101] and by the injection of GABA[37] or GABA agonists[102] into the ventral pallidum.

Carbachol injection into the unilateral PPN reduces spontaneous locomotor activities, and it also normalizes the increased locomotor activities produced by amphetamine injection into the ipsilateral nucleus accumbens.[104] Procaine injection into the bilateral PPN suppresses enhanced locomotion induced by carbachol injection into the bilateral hippocampus, but there are no changes after procaine injection into the bilateral medial dorsal thalamus. These findings suggest that spontaneous locomotion is not mediated by the ventral pallidal projections to the thalamus, but by the projections to the PPN.[105,106]

However, contradicting results have also been reported. Rats with the nucleus accumbens denervated by 6-hydroxy dopamine injection showed increased locomotion after amphetamine injection into the nucleus accumbens. Such locomotor activity was blocked by a lesion placed at the dorsomedial thalamus, but not by a PPN lesion. These findings suggest a possible role of the nucleus accumbens subpallidothalamic pathway in transmitting corticolimbic drive to the brainstem-spinal neuronal structures related to locomotion.[107]

In test animals, spontaneous locomotion occurs after postcollicular-premammillary transection, but not after postcollicular-postmammillary transection. In premammilary transection, one of the important factors for spontaneous locomotion may be the preservation of neuronal pathways descending from the subthalamic region to the brainstem.

High-current (larger than 70 μA) electrical stimulation of the posterior SN in cats with precollicular-postmammillary transection causes rhythmic extensor rigidity of the four limbs.[49] However, in animals with brain transection caudal to the SN, locomotion cannot be induced easily. The SN therefore seems to play an important role in the initiation of locomotion regulated by the PPN.[88,89]

In summary, internal needs to initiate locomotion, in order to approach subjects and explore the surroundings, originate in the limbic system or cerebral cortex. These outputs may be transmitted to the PPN directly or after polysynaptic contacts with the nucleus accumbens and ventral pallidum.[105,106,108,109] The neuronal pathways connecting the hippocampus to the PPN may trigger PPN tonic-firing cells and lead to initiation of locomotion. Such PPN neuronal activities seem to be under the control of the SN and STN.

The rhythmicity of locomotion: About 70% of the neurons in the areas ventral or dorsal to the PPN

show bursting activities related to the cycling frequencies of locomotion, and the remaining neurons show tonic activities. On the other hand, about 77% of the neurons in the PPN exhibit tonic activities, and the remaining neurons exhibit bursting activities. The tonic neurons are active either during, or before and after the locomotor activities. These neurons seem to turn-on or turn-off the rhythmic bursting neurons. They seem to fire transiently to initiate or stop locomotion.[79,85]

About half of the spinal projecting neurons in the medial ventral medullary region receive afferent fibers from the ipsilateral MLR.[91] Anatomically, the anterior and dorsal parts of this medullary area correspond to the nucleus reticularis gigantocellularis, and the posterior part to the nucleus reticularis ventralis. The dorsolateral parts of the nucleus reticularis gigantocellularis, pontis oralis and pontis caudalis give rise to the medial reticulospinal tract, whereas the ventrocaudal parts of the nucleus reticularis gigantocellularis and ventralis give rise to the lateral reticulospinal tract.[110-112]

Electrical stimulation of the medullary area giving rise to the medial reticulospinal tract induces monosynaptic excitation of the motoneurons supplying the flexor and extensor muscles of the limbs, the neck, and the back. Similar stimuli to the area giving rise to the lateral reticulospinal tract induces monosynaptic excitation and inhibition of the motoneurons supplying neck muscles, and a longer latency excitation of the limbs and back muscles. Rhythmic activities of the MLR and brainstem reticular nuclei, and their inhibitory and excitatory influences to the bilateral spinal motoneurons supplying flexor and extensor muscles after a different conduction delay, may enable rhythmic locomotor activities.[96,111-113]

Sleep

Rapid eye movement (REM) sleep is characterized by ponto-geniculo-occipital waves and a desynchronized electroencephalogram. Another major component of REM sleep is generalized muscle atonia except in the eye muscles.[79,114,115] Such atonia inhibits movement of the body during the REM phase, and may enable the maintenance of sleep.[116]

The cyclic occurrences of awakening, drowsiness, and desynchronized and synchronized sleep are mediated by efferent fibers to the thalamus: ascending cholinergic (from the PPN, LDTg, basal magnocellular nuclei), noradrenergic (from the locus coeruleus), serotonergic (from the dorsal and median raphe nuclei), and histaminergic (from the hypothalamus) efferent fibers to the thalamus. The midbrain cholinergic reticular formation is known to mediate desynchronized sleep and awakening.[117] While noradrenergic and serotonergic neurons undergo a marked decrease in discharge rates, increased firing of PPN neurons induces REM sleep.

Cholinergic stimulation of the mesencephalic tegmental area including the PPN increases the frequency of REM sleep. In contrast, electrolytic lesion, inhibition of the acetylcholine synthesis, or kainic acid injection into the bilateral dorsolateral ponto-mesencephalic tegmentum, reduces or eliminates REM sleep. The frequency of the ponto-geniculo-occipital wave correlates closely with the number of remaining cholinergic neurons in the PPN. Because of inability to maintain sleep, the percentage of waking time is significantly increased. Test animals also show increased twitches, movements, and postural shifts during sleep.[116,118-120]

Cervical muscle tone

In rats, high-frequency electrical stimulation of the unilateral PPN inhibits cortically-induced muscle activity bilaterally, and destruction of the PPN released the tonic and phasic inhibition of the bilateral axial muscles.[121] Isolated lesion of the ponto- mesencephalic tegmentum including the PPN prevents neck atonia and increases electromyogram (EMG) amplitude of the neck during sleep.[116] These may be a result of decreased excitatory PPN input to the inhibitory medullary reticular formation, with consequent disinhibition of neck muscle tone.[93]

Nociception

The PPN receives its main sensory inputs from the contralateral trigeminal receptive field, but also from other sensory-related neuronal structures, including the dorsal horn of the spinal cord and the cuneate nucleus.[32,122,123] In rats, cholinergic simulation of the PPN leads to anti-nociception for 5 to 10 minutes.[124] The PPN is the most sensitive site for nicotine-induced anti-nociception. Such PPN actions are mediated by controlling other neuronal structures as-

sociated with anti-nociception (e.g. the nucleus raphe magnus and periaqueductal grey substance).[125] The PPN also exercises control over reactions to painful stimuli.[38]

Startle reactions

The neuronal pathway mediating primary acoustic startle reactions consists of cochlea nucleus-ventral and dorsal nuclei of the lateral lemniscus-nucleus reticularis pontis caudalis- reticulospinal tract. A single cell recording study showed that 44% of the PPN neurons respond to auditory click stimuli.[126] A retrograde tracer study injecting dye into the PPN showed afferent fibers from the nucleus of lateral lemniscus.[32]

In rats, auditory stimuli evoked potentials in the PPN.[127] GABA antagonist (picrotoxin) injection into the subpallidum reduces prepulsive inhibition,[127,128] which is reduced or eliminated by electrolytic lesions of the PPN. The disruption of prepulsive inhibition correlates significantly with the extent of PPN damage. These findings suggest that the PPN modulates sensorimotor gating by transmitting information from the forebrain structures and the nucleus of the lateral lemniscus to the nucleus reticularis pontis caudalis.[129]

PATHOLOGICAL AND FUNCTIONAL CHANGES OF PPN IN THE ANIMAL MODELS AND IN THE PATIENTS WITH IPD AND PROGRESSIVE SUPRANUCLEAR PALSY (PSP)

PPN in animal models of parkinsonism

In response to amphetamine injection five of seven rats with about 75% of PPN cholinergic neuronal damage turned ipsilaterally; however, four of eight other rats with a similar degree of cholinergic PPN neuronal damage but more extensive damage to non-cholinergic PPN neurons turned contralaterally (3 turned ipsilaterally and 1 showed no directional preference).[130] Such inconsistent turning patterns suggest that distinct components in the PPN neurons projecting to the bilateral SN may play differentiated roles in the genesis of turning behavior.

In parkinsonian monkeys treated with MPTP, 2-deoxy glucose activity increased markedly in the PPN, most likely due to overactive inhibitory pallidal inputs.[131,132] In rats, injection of cholinergic agents into the SNc increases dopamine efflux in the ipsilateral striatum.[27,133] Taken together, these findings suggest that in IPD enhanced pallidal inhibition to PPN may aggravate striatal dopamine deficiency.

Interestingly, in rats overexcitation of PPN neurons induced by kainic acid injection into the PPN causes damage to the SN dopaminergic neurons.[134] However, it is uncertain whether a hypoactive PPN in patients with parkinsonism slows down the rate of progressive neuronal loss in the SNc.

PPN in patients with IPD and PSP

Pathological studies (Fig. 3): In addition to probable hyperactive pallidal inhibition of the PPN in IPD,[131,135] a pathological study on 8 patients with IPD showed about a 40% loss of large neurons within the PPNc.[136] All had Lewy bodies in the remaining PPNc neurons, suggesting a primary pathological change in the PPN. An immunohistochemical study of IPD brains also showed a 43% reduction in the total count of large PPN neurons containing substance-P, and a 28% loss in the LDTg corresponding to Ch6 of Mesulam.[26,137] However, Hirsch et al. could not find any evidence to suggest degeneration of the cholinergic neurons in the LDTg in IPD and PSP brains.[16] Such selective cholinergic neuronal damage has been interpreted as evidence for secondary change in the PPN following SN degeneration.[138]

The amount of neuronal loss in the PPNc appears to be correlated with the severity of parkinsonian symptoms and the severity of neuronal loss in the SNc.[136] There are strong inverse correlations between the age at death and the remaining substance-P immunoreactive neurons. However, the extent of PPNc neuronal loss is not correlated with the duration of IPD.[26,136] There is also considerable individual variation. In one study, 2 out of 6 IPD brains showed normal neuronal counts in the PPN.[16]

In PSP brains, pathological studies show significant cell loss in the mesencephalic and pontine cholinergic nuclei, including the PPNc (60−70% loss).[139-142] In addition, neurofibrillary tangles were found in about half of the remaining PPN neurons.[140,143] Interestingly, patients with Alzheimer's disease also have neurofibrillary tangles in the PPN, but there is no neuronal loss.[139,143]

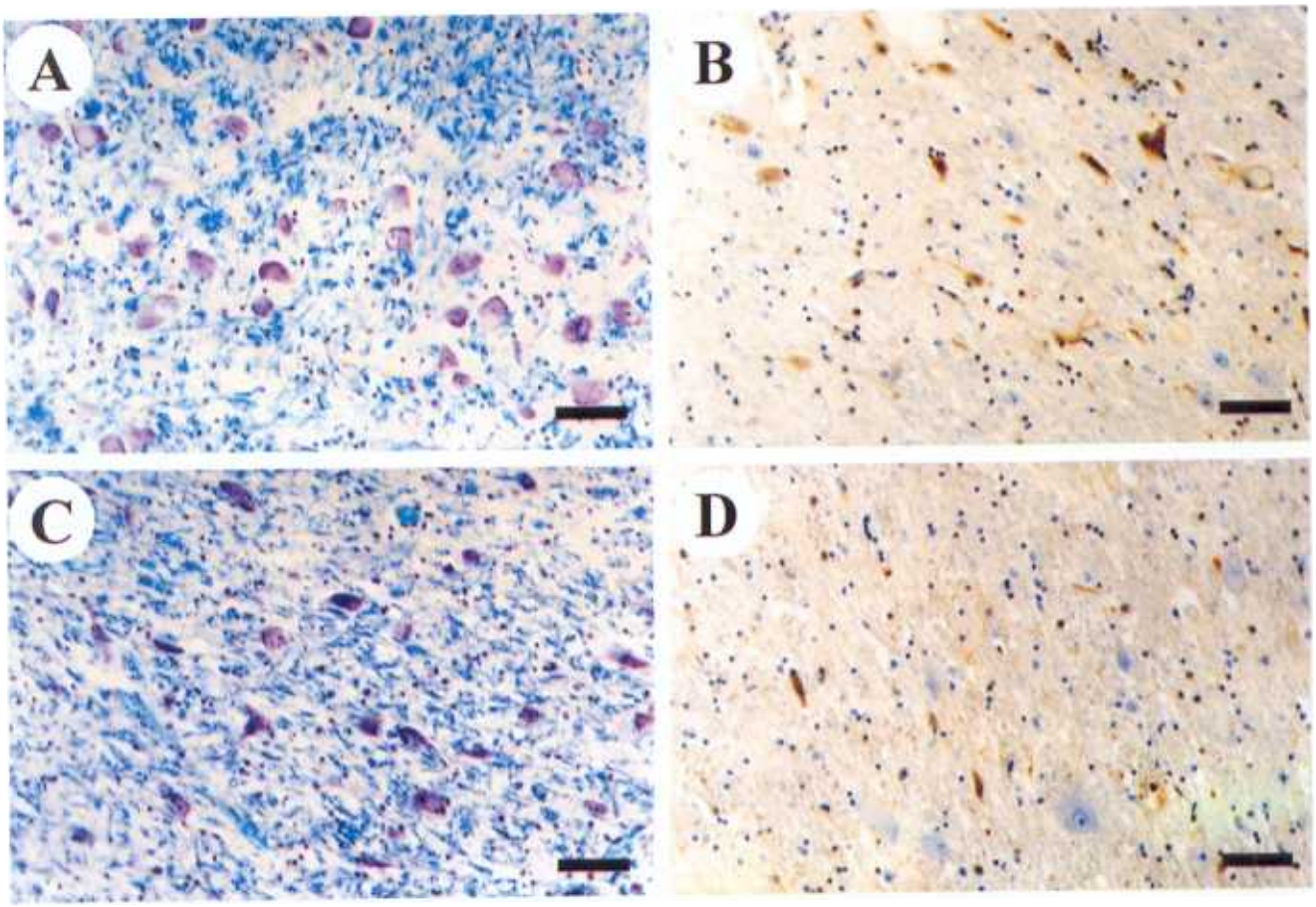

Fig. 3. Examples of luxol-fast blue and choline acetyl transferase positive pedunculopontine neurones in a control (A, B) and a patient with Parkinson's disease (C, D). The sections are taken at the mid level of the pedunculopontine nucleus. Bars represent 60 μm. Notice the reduced count and shrinkage of luxol-fast blue and choline acetyl transferase positive neurons in Parkinson's disease.

Secondary functional changes have also been reported in other basal ganglia nuclei following PPN degeneration. Autoradiographic studies showed increased binding of muscarinic cholinergic ligands in the GPm, suggesting supersensitivity of acetylcholine receptors.[144] ChAT activities in the SNc in IPD brains decreases to 15−25% of control values.[145] Because striatal cholinergic interneurons have no extrastriatal projections, such changes seem to be due to decreased cholinergic innervation from the PPN to the GPm and SNc.[146]

Symptomatic correlation:

Gait disturbances; Gait ignition failure, freezing, subcortical dysequilibrium and falls while walking can be seen frequently in patients with PSP or advanced IPD.[147] These gait disturbances are often resistant to levodopa treatment.[4] Degeneration of the SN and PPN seems to be one of the possible causes of loss of rhythmicity and sudden freezing while walking in patients with parkinsonism. In IPD, overactive pallidal and STN inhibitory inputs to the PPN may aggravate hypoactivity of the PPN due to neuronal loss.

Rigidity; Abnormal reciprocal inhibition has been proposed as one of the mechanisms possibly responsible for rigidity in parkinsonism. In PD, Ia inhibitory interneurons are more active and excitable compared to controls. In contrast, the degree of decreased Ib inhibitory interneuron activity is correlated with clinical severity of parkinsonism. Spinal interneurons are under the strong control of descending supraspinal inputs. The PPN, which is clearly damaged in PD, sends efferent fibers to the reticular nucleus. In patients with PD, excitatory reticulospinal inputs to the Ib interneurons are altered.[148]

Sleep and related disorders; Patients with IPD

have a shorter duration of REM sleep, but have longer non-REM sleep (stage I or II) than controls.[2] About half of 95 patients with IPD had poor sleep maintenance, and such patients more frequently suffered pain and depression than those without sleep disturbances.[3] In a study, all 10 patients with PSP suffered from severe insomnia; they spent 2 to 6 hours awake per night, corresponding to 50% wakefulness in bed. In the early stage of the disease, patients had delayed onset sleep, but this changed to fragmentation of sleep as the disease progressed. They also had significantly decreased total duration of REM sleep, and in 5 cases rapid eye movements during REM sleep were reduced.[149]

Failure to suppress locomotion during the transitional period from stage 4 sleep to REM sleep results in sleepwalking.[150] Interestingly, about 7% of patients with IPD are a sleepwalkers.[3] Among 29 men older than 50 years initially diagnosed with idiopathic REM sleep behavior disorder, about one third developed parkinsonism after a mean interval of 12.7 years from the onset of the REM sleep behavior disorder.[151]

Stimulation of the MLR either enhances or suppresses respiration.[152,153] One study including 20 patients with IPD and parkinsonism revealed that all patients had more apneic episodes than controls, and that patients with severe deficits experienced more apneic episodes.[2] Aldrich et al. found that 2 out of 10 PSP patients had sleep apnea, and they awoke more frequently than the other eight.[149]

Degeneration of the PPN and other cholinergic, adrenergic, or noradrenergic brainstem nuclei may be the cause of sleep disturbances and sleep-related disorders in IPD and other forms of parkinsonism.[151] However, discomfort due to immobility, nocturnal disorientation, and frequent daytime naps may be another possible causes of sleep disturbances in IPD and PSP.[149]

Eye movement abnormalities and cervical dystonia in PSP; Several clinical or pathological studies have implicated focal pontine or midbrain lesions in craniocervical dystonia.[154-156] PPN stimulation induces rapid eye movements and neck atonia. This suggests that hypofunction of the PPN due to degenerative changes is one of the possible causes of the eye movement abnormalities and neck dystonia seen in patients with PSP.[6,114,157] However, animal studies *(see above)* suggest that eye movement abnormalities and cervical dystonia in PSP are associated with widespread neuronal degeneration over the PPN, and more likely to the striato-nigro-collicular, tecto-oculomotor, and tecto-spinal pathways.[116]

Pain; About half of patients with IPD have primary sensory symptoms. In about 20%, sensory symptoms precede parkinsonian motor deficits. The majority has intermittent, poorly localized, dull pain with tightness. They also may have burning paresthesia, tingling, pins and needles, and numbness.[158] Such patients frequently have akineto-rigid type IPD.[3] However, the pain does not seem to be a secondary manifestation of rigidity, tremor, or the other motor deficits of IPD. No single treatment is effective for such pain. Snider et al. postulated that the pain may be related to central nervous system dysfunction.[158] Goetz et al., however, denied central sensory system dysfunction, since somatosensory evoked potentials were normal in IPD patients.[3]

Startle reaction; Patients with IPD show decreased habituation of P1 auditory potentials evoked by two-click stimuli with mid-latency. Less habituation was observed in patients with more severe parkinsonian deficits.[159] In patients with PSP, auditory startle reactions were absent or occurred after a longer latency than in controls. On the other hand, patients with IPD showed a normal pattern of startle reaction, but the latency of the startle reactions was delayed.[160]

POSSIBLE MECHANISMS FOR THE INCONSISTENT RESULTS FOLLOWING STEREOTAXIC BRAIN SURGERY IN IPD

Although stereotaxic thalamotomy targeted at the VL nucleus may destroy pallidothalamic inputs consist of the lenticular fasciculus and ansa lenticularis, consistent improvement was observed only for tremor and rigidity.[161,162] Similar results have been reported following anterodorsal pallidotomy.[7] Excellent results have been reported from posteroventral pallidotomy for severe IPD.[8,163] In patients with IPD, and in MPTP treated parkinsonian monkeys, subthalamotomy has also resulted in marked improvement of akinesia and complete disappearance of tremor and rigidity.[164-166] These findings suggest that the abnormal neuronal information responsible for tremor and rigidity is mediated by the pallido-thalamo-cortical pathway.[167] However, the neuronal circuits responsi-

ble for akinesia and gait disturbances seem to leave the pallido-thalamic pathways before they reach the thalamic targets.[162]

These inconsistent results of pallidotomy at different target sites may be due to the topographical organization of the GPm.[162] Stereotaxic lesions located in different parts of the GPm may cause differentiated amounts of damage to the pallidofugal fibers (*GPm-PPN and GPm-thalamus*), pallidopetal fibers (*putamen-GPm, caudate nucleus-GPm, PPN-GPm, and STN-GPm*) and the fibers passing through the GPm (*striatum-SN, SN-striatum, and lateral GP-STN*), as well as to the pallidal neurons themselves.[168]

Compared to anterodorsal pallidotomy, posteroventral pallidotomy is more likely to cause damage to the putamino-pallidal fibers and their pallidal target cells, but not to the caudato-pallidal fibers, which mainly terminate in the dorsal part of the pallidum. More extensive damage to the pallidal cells giving rise to pallidofugal fibers may also occur after posteroventral pallidotomy. The neuronal fibers passing through the caudal part of the GPm, such as striatonigral, nigrostriatal, and lateral GP-STN pathways, are more likely to be damaged. In addition to such direct damage, subsequent severe secondary degeneration in the VL thalamic nucleus and STN seem to occur more frequently after posteroventral pallidotomy.[40-42,46,47,168,169] The STN sends efferent fibers to the GPm, SN and PPN.[71] Subthalamotomy may disinhibit the PPN directly, by the disruption of the inhibitory STN inputs to the PPN, and indirectly, by decreasing excitatory STN input to the SN and GPm.

CONCLUDING REMARKS

In many cases, parkinsonian tremor and rigidity can be managed reasonably well by levodopa treatment, thalamotomy, or anterodorsal pallidotomy. Thalamotomy is also effective for levodopa-induced dyskinesia. The final basal ganglia output responsible for such movement disorders seems to be mediated via the thalamo-cortical pathway. However, patients with IPD or other forms of parkinsonism also suffer from dopamine-resistant parkinsonian deficits including akinesia, gait disturbances, primary sensory symptoms, and sleep disturbances.

The PPN operates as an interface between the cortico-striato-pallidal and limbic-ventral striatopallidal circuits. The PPN controls basal ganglia circuits directly, by its efferent fibers to the SN and STN, and indirectly, by efferent fibers to the paramedian-intralaminar thalamic neurons projecting to the striatum and frontal cortex. It sends descending fibers to pontomedullary reticular formation and spinal cord (Fig. 1). Animal studies have suggested an important role of the PPN in the initiation, acceleration, deceleration, and termination of locomotion. Other experimental and pathological studies have provided some evidence suggesting causal relationships between neuronal loss in the PPN and sleep disturbances, sleep-related disorders, abnormal auditory startle reactions, and spontaneous unexplained sensory symptoms in IPD and PSP.

In primates, the most profuse basal ganglia input to the PPN originates from the ventral part of the GPm. Thus, in IPD and PSP, overactive pallidal inhibitory input to the PPN, and neuronal loss in the PPN itself, result in PPN hypofunction. Posteroventral pallidotomy or subthalamotomy may reduce the overactive pallidal inhibitory input to PPN neurons, and result in disinhibition of the PPN. This state may lead to facilitation of transmission of limbic information to the brainstem reticular nuclei, and consequently improve locomotor deficits. Disinhibited the ascending PPN input to the thalamus may restore cyclic thalamo-cortical activation, and alleviate sleep disturbances.

The PPN is not the only neuronal structure responsible for dopamine-resistant parkinsonian deficits, however, and widespread brainstem nuclei degeneration seems to be involved. Nevertheless, the PPN does seem to play an important role in the genesis of a wide range of dopamine-resistant parkinsonian deficits.

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