REVIEW ARTICLE

The pedunculopontine nucleus and Parkinson’s disease

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Summary

Akinesia and gait disturbances are particularly incapacitating for patients with Parkinson’s disease. The anatomical and physiological substrates for these disturbances are poorly understood. The pedunculopontine nucleus (PPN) is thought to be involved in the initiation and modulation of gait and other stereotyped movements, because electrical stimulation and the application of neuroactive substances in the PPN can elicit locomotor activity in experimental animals. Glutamatergic neurones of the PPNd (pars dissipatus) are thought to be important regulators of the basal ganglia and spinal cord. The other component of the PPN, the cholinergic pars compacta (PPNc), is a principal component in a feedback loop from the spinal cord and limbic system back into the basal ganglia and thalamus. Electrophysiological studies suggest that ‘bursting’ glutamatergic PPNd neurones are related to the initiation of programmed movements while non-bursting cholinergic PPNc neurones are related to the maintenance of steady-state locomotion. Furthermore, since patients with Parkinson’s disease have significant loss of PPN neurones and experimental lesions in the PPN of normal monkeys result in akinesia, the degeneration of PPN neurones or their dysfunction may be important in the pathophysiology of locomotor and postural disturbances of parkinsonism. The goal of this review is (i) to highlight the anatomical connections and physiological attributes of the PPN, (ii) to discuss how the function of these connections may be altered in the parkinsonian state, and (iii) to speculate how present and potential future therapy directed to the PPN might improve akinesia and gait difficulties in parkinsonian patients.

Keywords: Parkinson’s disease; pedunculopontine nucleus; akinesia; gait; posture

Abbreviations: GABA = γ-aminobutyric acid; GPi = globus pallidus interna; IPSP = inhibitory postsynaptic potential; NMDA = N-methyl-D-aspartate; PPN = pedunculopontine nucleus; PPNc = pedunculopontine nucleus, pars compacta; PPNd = pedunculopontine nucleus, pars dissipatus; SNc = substantia nigra pars compacta; SNr = substantia nigra pars reticulata; SP = superior cerebellar peduncle; STN = subthalamic nucleus

Introduction

Locomotion in Parkinson’s disease

Gait disturbances are major impediments for parkinsonian patients (Murray et al., 1978; Morris et al., 1994, 1996). Although slowness of movement (bradykinesia) may affect all phases of gait, it is the failure of gait initiation (gait akinesia) which can be a particularly incapacitating problem. Gait initiation (the phase between motionless standing and steady-state locomotion) can be divided into a movement preparation period and a movement execution period (Brenière and Cuong, 1991). Gait initiation involves a highly stereotyped pattern of limb and trunk submovements with changes in posture (Elble et al., 1994). Although a number of kinetic studies have focused on steady-state locomotion, studies on gait initiation in Parkinson’s disease are few. It has been proposed that two types of difficulty can contribute to gait akinesia in Parkinson’s disease: (i) slowed movements and prolonged motor preparation times, leading to a delay in the execution of an otherwise preserved sequence of submovements (i.e. a problem in motor planning in which the patient is unable to call up or run an already-formed and preserved gait-initiation motor programme); and (ii) a problem in the ability to form the normal sequence of
submovements that compose the initiation of normal gait (i.e. a problem in motor programming in which there is a loss of or an inability to form the appropriate set of submovements or subroutines that make up the actual gait-initiation motor programme that otherwise should be available to be called up during motor planning) (Marsden, 1987; Rosin et al., 1997).

Studies of steady-state locomotion in Parkinson’s disease have supported alterations in both motor programming and motor planning (Knutstson, 1972; Stern et al., 1983; Forssberg et al., 1984; Dietz, 1993). Studies on gait initiation have suggested that the problems with gait initiation in Parkinson’s disease are due primarily to faulty motor planning that impedes the calling up of otherwise relatively preserved gait-initiation motor programmes (Rosin et al., 1997). Others have demonstrated that patients may also suffer from altered sensory feedback processing that can effectively interfere with gait initiation (Rogers and Chan, 1988; Horak et al., 1992).

In patients with advanced Parkinson’s disease, akinesia or ‘freezing’, the failure of willed movement to occur, is often only mildly improved by dopaminergic medication (Pullman et al., 1988; Starkstein et al., 1989) or unilateral surgical intervention (Lang et al., 1997; Lozano and Lang, 1998). The pathological substrates of gait and postural disturbances in parkinsonism are poorly understood, but recent observations suggest that dysfunction of the pedunculopontine nucleus (PPN) may be important.

The upper brainstem contains neurones which control axial and proximal limb musculature for gait through their projections to the lower brainstem and spinal cord via bilateral, midline, descending pathways. These brainstem nuclei are, in turn, under the influence of descending inputs from basal ganglia nuclei [globus pallidus interna (GPi); subthalamic nucleus (STN); substantia nigra pars reticulata (SNr)]. Because the function of these basal ganglia structures is markedly disrupted in parkinsonism, the brainstem motor areas to which they project and which they control may also be dysfunctional. Hence, interventions which block the abnormal activity of the basal ganglia in parkinsonism, including surgical lesions and high-frequency stimulation of basal ganglia targets, are potential ways of restoring the normal function of the brainstem centres which control locomotion. Recent attention to the brainstem areas involved in the control of locomotion has focused on the PPN. Although considerable animal data are available, little is known of the function of this nucleus in humans or to what extent observations in experimental animals are relevant to humans. Furthermore, studies on the anatomical connections
and physiology of the PPN are often incomplete, and are difficult to interpret because of methodological limitations, which often produce controversial and even contradictory interpretations. Despite these difficulties, which are sometimes serious, there is a large body of evidence supporting the role of the PPN in locomotion. The involvement of the PPN in human locomotion is supported by the observation of Masdeu and colleagues, who described the inability of a patient to stand and to generate stepping after a haemorrhage into the tegmentum of the posterior midbrain (Masdeu et al.,

Fig. 1 Axial sections through the brainstem showing cellular architecture (left) and tracts (right) at (A) intercollicular level (rostral extent of PPN) and (B) inferior collicular level (caudal extent of PPN). The PPNd is labelled 8 in A and the PPNc is labelled 9 in B. (A) Intercollicular level (rostral extent of PPN). 1 = nucleus intercollicularis; 2 = griseum centrale mesencephali; 3 = nucleus paralemniscalis; 4 = nucleus centralis colliculi inferioris; 5 = nucleus mesencephalicus nervi trigemini; 6 = nucleus nervi trochlearis; 7 = nucleus cuneiformis; 8 = nucleus tegmentalis pedunculopontinus, pars dissipata (PPNd); 9 = substantia nigra, pars compacta; 10 = nucleus interpeduncularis; 11 = nucleus pontis; 12 = commissura colliculi inferioris; 13 = brachium colliculi inferioris; 14 = fasciculus longitudinalis dorsalis; 15 = tractus mesencephalicus nervi trigemini; 16 = fasciculus anterolateralis; 17 = tractus tectospinalis; 18 = tractus trigeminohalamicus dorsalis; 19 = nervus trochlearis; 20 = fasciculus longitudinalis medialis; 21 = tractus tegmentalis centralis; 22 = lemniscus medialis; 23 = pedunculus cerebellaris superior; 24 = decussatio pedunculorum cerebellarum superiorum; 25 = pedunculus mamillaris; 26 = tractus parietotemporopontinus; 27 = tractus pyramidalis; 28 = tractus frontopontinus; 29 = fibrae pontocerebellares. (B) Inferior collicular level (caudal extent of PPN). 1 = nucleus intercollicularis; 2 = colliculus inferior, nucleus centralis; 3 = colliculus inferior, zona lateralis; 4 = griseum centrale mesencephali; 5 = locus coeruleus; 6 = nucleus mesencephalicus nervi trigemini; 7 = nucleus cuneiformis; 8 = corpus parabigeminum; 9 = nucleus tegmentalis pedunculopontinus, pars compacta (PPNc); 10 = nucleus centralis superior; 11 = substantia nigra, pars compacta; 12 = nucleus interpeduncularis; 13 = nuclei pontis; 14 = commissura colliculi inferioris; 15 = fasciculus longitudinalis dorsalis; 16 = nervus trochlearis; 17 = tractus mesencephalicus nervi trigemini; 18 = lemniscus lateralis; 19 = tractus tectopontinus; 20 = fasciculus anterolateralis; 21 = fasciculus longitudinalis medialis; 22 = tractus tegmentalis centralis; 23 = lemniscus medialis; 24 = pedunculus cerebellaris superior; 25 = decussatio pedunculorum cerebellarum superiorum; 26 = fibrae corticotenatalis; 27 = pedunculus mamillaris; 28 = fibrae pontocerebellares; 29 = tractus parietotemporopontinus; 30 = tractus pyramidalis; 31 = tractus frontopontinus. From Nieuwenhuys et al. (1998), with permission.
Although they emphasized damage to the PPN as a probable cause, the damage appeared to extend beyond the boundaries of the PPN.

**Anatomy of the PPN**

The PPN consists of a neurochemically and morphologically heterogeneous population of neurones. In the human brain, the PPN is bounded on its lateral side by fibres of the medial lemniscus and on its medial side by fibres of the superior cerebellar peduncle and its decussation (Olszewski and Baxter, 1982; Geula et al., 1993) (Fig. 1). Rostrally, the anterior aspect of the PPN contacts the dorsomedial aspect of the posteralateral substantia nigra, while the retrolubar field borders it dorsally. The most dorsal aspect of the PPN is bounded caudally by the pontine cuneiform and subcuneiform nuclei and ventrally by the pontine reticular formation. The most caudal pole of the PPN is adjacent to neurones of the locus coeruleus.

Two subdivisions of the PPN have been recognized on the basis of cell density. The pars compacta of the PPN (PPNc) is located within the caudal half of the nucleus in its dorso-lateral aspect. Cells of the subnucleus pars dissipatus (PPNd) are distributed sparsely within the superior cerebellar peduncle and central tegmental tract. The pars compacta and dissipatus have been described in humans, monkeys and subprimates (Mesulam et al., 1983; Geula et al., 1993; Lavoie and Parent, 1994a). The number of cholinergic neurones within the PPN in humans has been estimated at between 10 000 and 15 000 (Garcia-Rill et al., 1995, 1996). Cholinergic PPNc neurones are clustered along the dorso-lateral border of the superior cerebellar peduncle (SP) at trochlear nucleus levels, whereas those in the PPNd are scattered along the SP from midmesencephalic to midpontine levels. In the human brainstem, the cholinergic neuronal population of the PPN (Ch5) constitutes >90% of the neuronal population of the PPNc, and 25–75% in the PPNd (Mesulam et al., 1989).

The second prominent neuronal population contained within the traditional boundary of the PPNd is glutamatergic (Lavoie and Parent, 1994a; Rye et al., 1995b, 1996). Lavoie and Parent found that, at the brainstem level of the trochlear nucleus, ~40% of monkey PPN cells express cholinergic and glutamatergic immunoreactivity (Lavoie and Parent, 1994a). Additional neuronal types contained within the traditional boundary of the non-human PPN include a dopaminergic population (Rye et al., 1987), a noradrenergic group and a small group of GABAergic interneurones (Jones, 1991). Despite numerous studies, however, there has been no consensus regarding the average number of PPNc or PPNd neurones or the breakdown of cell types in the PPNd found in humans or other species.

**Inputs to the PPN**

Anatomical and electrophysiological studies on non-humans have identified many putative afferents to the mesopontine tegmental region containing the PPN. However, because of its neurochemical heterogeneity and close apposition to several other functionally distinct regions and fibre tracts, it has been difficult to determine precisely which afferents actually terminate in the PPN and, of these, which terminate on cholinergic versus non-cholinergic PPN neurones. Very little is known about the inputs and outputs of the human PPN.

Afferents from the GPi and the SNr are the most widely studied and established connections to the primate PPN (Shink et al., 1997). Pallidal efferent pathways to the PPN and midbrain tegmentum descend along the pallidotegmental tract, which runs dorsomedially from the globus pallidus, past the subthalamic nucleus and into the midbrain tegmentum near the ventrolateral border of the red nucleus. Recent anatomical studies on humans and other primates have shown that the pallidal projections appear to terminate preferentially on the non-cholinergic cells of the PPNd and largely avoid the cholinergic neurones of the PPNc and PPNd (Rye et al., 1995b; Shink et al., 1997). Projections from the SNr also appear to terminate mainly but not exclusively on the non-cholinergic cells of the PPNd in rats (Kang and Kitai, 1990; Spann and Grofova, 1991). This has not been shown in primates. It is also not known to what extent GPi and SNr inputs are segregated to separate territories within the PPN or converge onto the same PPNd neurones. The pallidal and SNr projections to the PPN are GABAergic (Noda and Oka, 1986; Granata and Kitai, 1991). Studies have shown that >80% of GPi neurones send axon collaterals to both the ventrolateral nucleus of the thalamus and the PPN in monkeys (Haruno and Filion, 1982). Indeed, the axonal branch of GPi neurones projecting to the PPN in non-human primates is of larger diameter than the thalamic branch (A. Parent, personal communication). This suggests that the PPN may be the principal target of pallidal outflow. This collateralization has not been shown for SNr inputs to the PPN.

Glutamatergic inputs to PPN from the STN have been described in rats (Hammond et al., 1983; Jackson and Crossman, 1983; Kita and Kitai, 1987; Granata and Kitai, 1989; Steininger et al., 1992), but not in primates. The different subpopulations of rat PPN neurones that serve as targets for the STN inputs have not been established. Similarly, the nucleus accumbens provides significant inputs to the rat PPN (Groenewegen et al., 1993). However, very little is known about the nature of this connection in primates.

Inputs from the cervical and lumbar segments of the spinal cord to the area of the PPN have been shown in the rat (Grunwerg et al., 1992) and cat (Hylden et al., 1985), but not in primates. These studies have suggested that cholinergic PPN neurones act as a relay station for spinal cord sensory afferents to the thalamus. The neurotransmitter system involved in this spinal input is unknown. The major putative inputs to the PPN from the basal ganglia and related structures the primate are summarized in Fig. 2.

A number of other putative afferents to the PPN in rats and cats (but not primates) have been proposed (but not firmly established because of non-specific uptake of tracers.
from surrounding midbrain structures) to arise from areas within the limbic system (amygdala, hypothalamus, zona incerta) and the ascending reticular activating system (raphe nuclei, locus coeruleus, laterodorsal tegmental nucleus, contralateral PPN), as well as from premotor and supplementary motor cortical areas (Monakow et al., 1979; Edley and Graybiel, 1983), the substantia nigra pars compacta (SNc) and the caudate, putamen, superior colliculus, basal forebrain and deep cerebellar nuclei. This work and the methods used have been reviewed recently (Reese et al., 1995; Winn et al., 1997). The significance of these projections is not understood.

**Outputs from the PPN**

Most information regarding PPN outputs comes from non-primate studies. The outputs of the PPN (Fig. 3) can be divided into descending and ascending components, with cholinergic and non-cholinergic neurones contributing to both. Although some PPN neurones have specific ascending projections and others specific descending projections, some collateralize and project in both directions (Rye et al., 1987; Spann and Grofova, 1991). The ascending projections of the PPN are much more prominent than the descending projections, although there is no consensus about their relative proportions or which subpopulations of PPN neurones (cholinergic versus non-cholinergic or PPNC versus PPND) contribute to the various output pathways. Furthermore, it has been estimated that ~40% of monkey PPN neurones project contralaterally to their basal ganglia targets (Lavoie and Parent, 1994b); the percentage has not been established for each individual basal ganglia target.

**Ascending projections**

Ascending PPN outputs project via the dorsal and ventral tegmental bundles, the dorsal tegmental pathway carrying the major cholinergic projection (Garcia-Rill, 1991). The majority of ascending cholinergic PPN neurones are thought to project to all thalamic nuclei in the rat (Hallanger et al., 1987; Rye et al., 1987), cat (Steriade et al., 1988) and monkey (Lavoie and Parent, 1994b), but especially to the associative and non-specific midline thalamic nuclei. In the rat it has been estimated that 60% of cholinergic PPN neurones project to the thalamus and that 90% of PPN inputs to the thalamus are cholinergic (Sofroniew et al., 1985). Similar quantitative data are not available for primates.

Ascending projections also provide dense innervation to the non-thalamic basal ganglia structures via the ventral tegmental bundle (Lavoie and Parent, 1994a, b, c). Neurons located in the core of the PPN (presumably PPNC neurones, although this is not clearly stated by Lavoie and Parent) are those that provide the most dense innervation of the basal ganglia. Labelling with anterograde tracers has shown that the SNc and the STN are by far the most densely innervated structures of the basal ganglia. PPN efferents reach their target sites in the basal ganglia by ascending along the
lenticular fasciculus and ansa lenticularis, which are the major output projection paths of the GPi.

Substantia nigra (SN). The PPN sends cholinergic projections to the dopamine-containing neurones of the SNc with a minor cholinergic contingent to the SNr in the rat (Woolf and Butcher, 1986; Scarnati et al., 1988). Recently, it has been shown that PPN cholinergic and glutamatergic neurones form synaptic contacts with dopaminergic neurones in the SNc in non-human primates and rats (Charara et al., 1996; Takakusaki et al., 1996). There are also studies which suggest that single PPN terminals in contact with SNc dopaminergic neurones may contain both glutamate and acetylcholine (Lavoie and Parent, 1994c; Charara et al., 1996). In the anaesthetized rat, electrical stimulation of PPN neurones leads to excitation of SNc neurones via a short-latency, direct, excitatory PPN–substantia nigra pathway and a less marked and rather sparse activation via a short polysynaptic pathway (Scarnati et al., 1984, 1986, 1987), probably involving non-cholinergic PPN neurones (Scarnati et al., 1986; Di Loreto et al., 1992). The proportion of PPN neurones projecting to the substantia nigra is ~40% in the rat and only 25% in the monkey (Gould et al., 1989; Lavoie and Parent, 1994c). The relative proportions of PPN outflow to the SNc versus the SNr and the subpopulations of PPN neurones giving rise to this projection have not been determined. The PPN may also be a source of GABAergic afferents to the SNc in primates (Charara et al., 1996).

Subthalamic nucleus (STN). The existence of a bilateral projection from the PPN to the STN has been documented in a number of species, including the rat (Woolf and Butcher, 1986), cat (Edley and Graybiel, 1983) and monkey (Lavoie and Parent, 1994b). These studies fall short of assessing the anatomical (PPNd versus PPNc) and neurochemical (cholinergic versus non-cholinergic) nature of this pathway, although in the rat these have been shown to be both cholinergic (Woolf and Butcher, 1986) or non-cholinergic (Lee et al., 1988) and excitatory (Hammond et al., 1983). Other studies in the rat suggest that PPN efferents to the STN and adjacent zona incerta are collaterals of PPN efferents to the pallidal complex (Hammond et al., 1983; Hallanger and Wainer, 1988).

Globus pallidus (GP). In the monkey, the PPN innervation of the pallidal complex is less dense than that of the STN and substantia nigra. Pedunculopallidal fibres travel back along both the ansa lenticularis and lenticular fasciculus and arborize more profusely in the monkey GPi than the globus pallidus externa (Lavoie and Parent, 1994b), as has been shown in the rat and cat. The neurotransmitter used by pedunculopallidal neurones has not yet been identified with certainty. In the human brain, the GP receives cholinergic innervation, the majority of which is thought to originate from brainstem cholinergic nuclei (Mesulam et al., 1983), but specific cholinergic innervation from PPN neurones has not been shown. Although excitatory responses after PPN stimulation were found in cat pallidal neurones (Gonya-Magee and Anderson, 1983), it was not clear which populations of PPN neurones were stimulated or which populations of pallidal neurones were activated.

Striatum. A pedunculostral projection has been shown in the monkey (Lavoie and Parent, 1994b). These PPN fibres are poorly arborized in most of the caudate nucleus and putamen. The chemical nature of this projection is unknown.

Other ascending targets. Other ascending targets thought to exist in non-primate species include the superior colliculus and a number of limbic structures (basal forebrain, hypothalamus, zona incerta, amygdala). These ascending connections have been reviewed recently (Inglis and Winn, 1995; Reese et al., 1995; Winn et al., 1997).

Descending projections

Although studied predominantly in non-primates, descending targets include several midbrain, pontine and medullary areas including several nuclei of the reticular formation, the deep cerebellar nuclei and the spinal cord (reviewed by Inglis and Winn, 1995; Reese et al., 1995). These descending projections are thought to collateralize extensively to caudal structures (Rye et al., 1988) as well as to the thalamus (Semba et al., 1990). The relative contributions of cholinergic and non-cholinergic neurones to the innervation of the medulla and spinal cord have been assessed only in the rat (Goldsmith and van der Kooy, 1988; Rye et al., 1988; Skinner et al., 1990) and cat (Edley and Graybiel, 1983). Most of the descending cholinergic PPN neurones travel a shorter distance to the medullary reticular formation, which in turn provides bilateral outputs to the spinal cord. The direct projection from the PPN to the cervical and thoracic cord is thought to be mainly non-cholinergic, although a small number of cholinergic PPN neurones may project as far as the spinal cord (Rye et al., 1988). Some of these descending projections are thought to terminate unilaterally in intermediate laminae of the cervical and thoracic cord and bilaterally in the central grey of the cervical cord, rather than directly on motor neurones (Goldsmith and van der Kooy, 1988; Rye et al., 1988). The major outputs from the PPN to the basal ganglia and related structures in the primate are summarized in Figs 2 and 3. In general, the ascending and descending projections of the PPN in the primate are similar to those in the cat and the rodent. However, again it should be pointed out that minimal data are available for humans.

Electrophysiological properties of PPN neurones

Types of PPN neurones

Intracellular recordings

Three types of PPN neurones have been identified on the basis of their electrophysiological membrane properties obtained by
intracellular recordings (Kang and Kitai, 1990; Takakusaki et al., 1996, 1997; Takakusaki and Kitai, 1997). Type I neurones are characterized by bursts of fast action potentials. The bursting (phasic) pattern of action potentials can be elicited by depolarizing current or by the offset of hyperpolarizing current, indicating that this type of neurone can shift into a bursting mode in response to either an excitatory or an inhibitory input. Morphologically, type I neurones are small to medium spindle-shaped or triangular cells with three to five primary dendrites. Type I neurones are dispersed throughout the extent of the PPN and are probably glutamatergic (Takakusaki et al., 1996).

As stated above, GABAergic pallidal and nigral efferents to the PPN project preferentially to non-cholinergic PPN neurones (Kang and Kitai, 1990; Spann and Grofova, 1991; Rye et al., 1995b; Shink et al., 1997). Several investigators have shown that electrical stimulation of the SNr evokes predominantly monosynaptic inhibitory postsynaptic potentials (IPSPs) and decreases the firing rate in PPN neurones in the anaesthetized rat (Granata and Kitai, 1991) and cat (Noda and Oka, 1984) and in rat brain slices (Kang and Kitai, 1990; Takakusaki et al., 1996). After a period of suppressed activity, PPN neurones can rebound with increased spike discharges (Kang and Kitai, 1990). Histochemical staining has shown that IPSPs can be recorded from both non-cholinergic and cholinergic PPN neurones by SNr stimulation (Kang and Kitai, 1990).

Type II neurones do not have burst-firing. Instead they fire single action potentials with large afterhyperpolarizations in response to injections of depolarizing current. This characteristic is suited to a relatively slow tonic repetitive firing pattern. Type II neurones are located in the rostral and middle sections of the PPN and in general are medium to large, fusiform or polygonal cells possessing five to seven primary dendrites. About 50% of type II neurones are cholinergic. Thus, there seem to be two electrophysiologically distinct populations of PPN neurones: ‘bursting’ (type I; likely glutamatergic) and ‘non-bursting’ (type II; 50% cholinergic). A third type of PPN neurone has characteristics of both type I and type II PPN neurones. A second group of investigators has also described three major classes of PPN neurones following intracellular recordings from thalamic-projecting, rhodamine-labelled PPN neurones in the guinea-pig slice preparation (Leonard and Llinás, 1988). These were similar to the three types described above in the rat.

**Extracellular recordings**

Extracellular spike discharges from PPN neurones have been observed in the anaesthetized rat (Hammond et al., 1983; Scarnati et al., 1987; Granata and Kitai, 1991; Ogura et al., 1997) and cat (Noda and Oka, 1984). In these animals, one group of cells had broad spikes with low and regular spontaneous firing rates (0.5–8 spikes/s). A second set of cells exhibited narrow spikes with higher discharge rates, ranging from 10 to 20 spikes/s (Scarnati et al., 1987). Preliminary experiments have suggested that ~75% of PPN neurones in rats have a regular pattern of activity (possibly corresponding to cholinergic neurones) and 25% a ‘bursting’ pattern (possibly corresponding to non-cholinergic neurones; Ogura et al., 1997). In awake cats, 25% of cells had broad spikes (2 ms duration) with a mean resting firing rate of 12 Hz, while 75% of cells had narrow spikes (0.7 ms duration) with a mean discharge rate of 24 Hz (Dormont et al., 1998). The cells with broad spikes and low discharge rates are thought to be cholinergic (Takakusaki et al., 1997) and probably correspond to the type II neurones described above. The other set of cells, with higher discharge rates, correspond to the non-cholinergic type I neurones. Similar extracellular recordings have been reported in awake monkeys (Matsumura et al., 1997). Recordings from the human PPN have not been reported.

The descending PPN projection to the spinal cord has been suggested to be a source of muscle tone control (Rye et al., 1988) and a pattern generator for locomotion (see below). Thus, PPN neurones may act as a pace-setter for firing (be it bursting or non-bursting) of their target neurones (Kang and Kitai, 1990). As described above, the PPN contains populations of neurones with intrinsic membrane properties that allow tonic or non-burst firing (type II, cholinergic) and those that allow phasic or burst firing (type I, non-cholinergic; Takakusaki et al., 1996). Thus, the membrane properties of the type II cholinergic neurones could allow tonic pace-setting (as in regulating the velocity of steady-state locomotion), whereas those of the non-cholinergic type I neurones could be involved in phasic pace-setting (i.e. in gait initiation). However, there is no direct evidence to support this. Since projections from the GPi and SNr seem to preferentially target the non-cholinergic PPN neurones and since this population of PPN neurones provides the prominent descending PPN outputs to the spinal cord (Rye et al., 1988), one could further speculate that pallidal and nigral connections to the type I (bursting, non-cholinergic) PPN neurones may be an important means by which the basal ganglia regulate the initiation of gait.

**Membrane receptors and pharmacology of PPN neurones**

Numerous neurotransmitters have been proposed to influence PPN neurones directly (Table 1). Data have been generated both in vitro and in vivo. In vitro studies have used experimental rat and guinea-pig slice preparations with bath applications or local microinjections of neuroactive agents. These studies provide strong evidence for the direct influence of a number of neuroactive agents on PPN neuronal activity. In vivo studies have observed animal behaviour in awake or anaesthetized rats or cats during intracerebral microinjections of various neuroactive agents. These studies provide behavioural information that may be of physiological significance, but the actual microinjection sites are
### Table 1 PPN pharmacology, electrophysiology and behaviour

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<td>Carbachol (AGO)</td>
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<tr>
<td>Mepyramine (H1-ANT)</td>
<td></td>
<td>No effect17</td>
<td></td>
</tr>
<tr>
<td>Cimetidine (H2-ANT)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Noradrenaline</td>
<td>RS, BA</td>
<td>↓ firing, hyperpolarization 2o to ↑ I(k)18</td>
<td></td>
</tr>
<tr>
<td>Opiates</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>µ-AGO</td>
<td>GPS, BA</td>
<td>↓ firing, hyperpolarization 2o to ↑ I(k)2</td>
<td>Blocks opiate effect2</td>
</tr>
<tr>
<td>Naloxone (ANT)</td>
<td></td>
<td></td>
<td>No effect2</td>
</tr>
<tr>
<td>κ-AGO, δ-AGO</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serotonin</td>
<td>RS/GPS, BA/MI</td>
<td>↓ firing, hyperpolarization 2o to ↑ I(k)4</td>
<td>Blocks serotonin effect1</td>
</tr>
<tr>
<td>Substance P</td>
<td>Awake rat, MI</td>
<td></td>
<td>↑ locomotion5</td>
</tr>
<tr>
<td>Glycine</td>
<td></td>
<td></td>
<td>No effects on locomotion4</td>
</tr>
<tr>
<td>Strychnine (ANT)</td>
<td></td>
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</table>


Anatomically localized by gross stereotaxic techniques and are only later documented by histochemical staining. This is an important consideration, since microinjections that are only 1–2 mm apart can give completely opposite behavioural effects (Garcia-Rill et al., 1990). No studies have combined microinjection and electrophysiological techniques in intact animals to obtain better functional targeting of the actual sites of microinjections with electrophysiological techniques while assessing behavioural responses. It should be noted that there have been many other reports of microinjections into the general region of the mesencephalic locomotor area or the lateral dorsal tegmental area. We will summarize only those thought to be specific to the PPN.

**Glutamate/NMDA**

In the guinea-pig brain slice, bath applications or microinjections of glutamate or N-methyl-D-aspartate (NMDA) caused dose-dependent depolarization and increased firing of cholinergic PPN neurones lasting up to several minutes (Sanchez and Leonard, 1994). These effects were blocked by the appropriate antagonists (Table 1). In behavioural studies, microinjections of glutamate agonists in the area of the rat PPN generally increased locomotion (Milner and Mogenson, 1988; Niijima and Yoshida, 1988). In an *in vivo* study using anaesthetized precollicular-transected rats, the PPN injection site was further defined functionally by locomotion induced by electrical stimulation (Garcia-Rill et al., 1990). In these experiments, additional injections of NMDA could drive stepping from a walk to a trot to a gallop. These effects were blocked in a dose-dependent manner by specific NMDA antagonists. Since they occurred in rats with a transection at the upper brainstem, the effects were independent of brain structures rostral to the cut. These studies suggest that the application of glutamate agonists excites cholinergic PPN neurones and leads to increased locomotion. However, there have been no reports showing increased locomotion coincident with increased PPN.
activity during injections of glutamate agonist. One group showed increased activity of presumed PPN neurones with local microinjections of glutamate in the anaesthetized rat (Hammond et al., 1983). However, very high concentrations of glutamate (1 mol/l) were required and no behavioural observations were made. It has been shown that microinjections of glutamate agonists into the area of the PPN increases the firing rate of presumed dopaminergic neurones of SNC via a cholinergic pathway (Clarke et al., 1987) and elicits the turning behaviour associated with an increase in dopamine turnover in the neostriatum (Nijjima and Yoshida, 1988; Hernandez-Lopez et al., 1992).

### Acetylcholine

In the guinea-pig brain slice, microinjections of carbachol (an acetylcholine agonist) caused dose-dependent hyperpolarization and decreased firing of cholinergic PPN neurones (Serafin et al., 1990; Leonard and Llinás, 1994). These effects were blocked with atropine (a muscarinic antagonist). In a number of behavioural studies, investigators showed that microinjections of carbachol into the rat PPN area decreased locomotion with a similar time-course of effect (a delay of a few minutes and a duration of 10–30 min) (Brudzynski et al., 1988; Milner and Mogerson, 1988; Garcia-Rill et al., 1990; Mathur et al., 1997). These effects could also be blocked by antimuscarinics (atropine or scopolamine) but not by anti-nicotinics. These studies suggest that the application of cholinergic agonists inhibits cholinergic PPN neuronal activity and leads to decreased locomotion. There have been no reports of decreased locomotion coincident with decreased PPN neuronal activity during injections of acetylcholine agonists. Cholinergic input onto PPN neurones appears to originate in the contralateral PPN and ipsilateral laterodorsal tegmentum in the rat (Fibiger and Semba, 1988).

### GABA

Bath applications of bicuculline (a GABA antagonist) in rat brain slices blocked the IPSPs in cholinergic PPN neurones that were evoked by electrical stimulation of the SNr (Kang and Kitai, 1990). Microinjections of bicuculline or picrotoxin (GABA antagonists) into the PPN area increased locomotion in a dose-dependent manner and with similar time-courses of effect, whereas muscimol (a GABA agonist) inhibited locomotion in intact rats (Childs and Gale, 1984; Milner and Mogenson, 1988; Garcia-Rill et al., 1990). These effects were unaltered in rats with the brainstem hemitransected just rostral to the PPN (Childs and Gale, 1984). In addition, in the neuroleptic-induced catalepsy rat model of parkinsonism, microinjections of picrotoxin (a GABA antagonist) into the PPN area increased locomotion with a similar time-course (Miwa et al., 1996). Furthermore, in freely moving cats in which the PPN was physiologically identified with single-unit recordings, muscimol caused a similar arrest of motor performance (Condé et al., 1998). Unfortunately, any concomitant effects on PPN neuronal activity were not reported.

### Others agents

A number of other neuroactive agents (including serotonin, noradrenaline, histamine and opiates (Table 1), are thought to influence the firing of PPN neurones. All of these, except histamine, may be inhibitory. Even less is known, however, concerning the relative importances of these other agents, their distribution and origin, and the specific cell types of the PPN with which they are in synaptic contact (i.e. cholinergic versus non-cholinergic or bursting versus non-bursting). Immunohistochemical and electron microscope studies in rats have shown that serotonergic afferents onto cholinergic PPN neurones apparently arise in the raphe nuclei (Honda and Semba, 1994). Possible excitatory histaminergic afferents from the posterior hypothalamus to the PPN (Khatibe et al., 1990) have been implicated in an H1 receptor-mediated arousing action of histamine. Other possible neurotransmitter inputs to the PPN include glycine and galanin. Glycine-immunoreactive fibres and terminals have been observed apposed to cholinergic neurones in the cat PPN (Fort et al., 1993). The peptide neurotransmitter galanin has been localized in axonal fibres and terminals in the region of substance-P-containing neurones of the human PPN (Gai et al., 1993). Microinjection of substance P into the rat PPN area increases locomotion (Garcia-Rill et al., 1990). The physiological significance of these connections remains unknown.

In summary, the studies suggest that GABA and acetylcholine decrease cholinergic PPN activity and diminish locomotion, while glutamate increases cholinergic PPN activity and increases locomotion (Table 2). No studies have shown simultaneous effects on PPN neuronal activity or behavioural effects. The glutamate and GABA effects were similar in transected animals, suggesting that the expression of PPN outputs is not dependent upon ongoing influences from the basal ganglia. Interactions of these different neurotransmitter systems at the level of the PPN have also been shown. In studies on rats, carbachol and GABA have

<table>
<thead>
<tr>
<th>Neurotransmitter system</th>
<th>Cholinergic PPN neuronal activity</th>
<th>Locomotion</th>
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<tbody>
<tr>
<td>Glutamate</td>
<td>↑↑</td>
<td>↑↑</td>
</tr>
<tr>
<td>Acetylcholine</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>GABA</td>
<td>↓</td>
<td>↓</td>
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</table>

Both cholinergic and GABAergic systems seem to inhibit cholinergic PPN neuronal activity and diminish animal locomotion, whereas the glutamatergic system seems to increase cholinergic neuronal activity in the PPN and to increase animal locomotion.
been shown to block NMDA-induced locomotion (Garcia-Rill et al., 1990).

In general, there has been little reproduction of experiments from different laboratories. If attempted, they suffer from great differences in the methods and drug concentrations used. This has resulted in great variability of results, especially in the time-course of effects. Work has concentrated mainly on the cholinergic PPN neurones (as identified by electrophysiological properties in slices or postinjection histochemistry in behavioural studies), with little emphasis on the non-cholinergic population of PPN neurones. In addition, studies have been limited to non-primate species, and there has been only one study in a rodent model of Parkinson’s disease (Miwa et al., 1996).

Although the in vitro experiments summarized above suggest that the various types of receptors are present and function in PPN neurones, they do not give conclusive proof. Receptor-localization studies have established the presence of NMDA-sensitive receptors in the area of the PPN (Stone and Burton, 1988), but have not confirmed their actual existence on PPN neurones. Muscarinic cholinergic (M₂, M₃ and M₄) receptors were reported to be located on monkey and human cholinergic PPN and laterodorsal tegmentum neurones (Rye et al., 1995a), the M₂ receptor possessing characteristics consistent with an inhibitory autoreceptor, although the physiological role of these receptors is unknown. It has been proposed that the psychotropic actions of antimuscarinics occur via M₂ autoreceptors on cholinergic PPN cells, whereas their antiparkinsonian effects occur via M₁ receptors in the forebrain (Yeomans, 1995). Glycine receptors have also been demonstrated in the area of the human PPN (Probst et al., 1986).

The role of the PPN in locomotion
The mesencephalic locomotor region

The PPN is believed to be part of the so-called mesencephalic locomotor region. This is a functionally defined area of the brainstem within which it is possible to elicit controlled locomotion (locomotion in which increasingly higher levels of electrical stimulation drive the frequency of stepping from a walk to a trot to a gallop) on a treadmill in decerebrate animals including the cat (Garcia-Rill and Skinner, 1987a, b), rat (Garcia-Rill, 1990) and possibly the monkey (Eidelberg et al., 1981).

Although the optimal sites for the induction of locomotion appear to be within the cholinergic neurone mass of the PPNc (Garcia-Rill et al., 1987), there are several brainstem regions, including prominent sensory nuclei, which can be stimulated to initiate locomotion (for a recent review, see Reese et al., 1995). Each of these areas possesses direct outputs to the spinal cord (the site of putative locomotor pattern generators) and none of these areas can be considered to be specific to locomotion.

Neural networks have been used to model brain function during locomotion in all classes of vertebrates (Grillner, 1985). Thus, the same mesopontine and diencephalic centres initiate locomotion in lampreys and primates, through the activation of lower brainstem reticulospinal neurones. These, in turn, activate spinal networks of neurones which generate the motor pattern, be it swimming or walking. Sensory feedback is an integral part of the control system and helps to adapt the motor pattern to external events. This sensory input is important for the initiation of movements and for providing ongoing feedback for the maintenance of movement. Details of the cellular and molecular function of this network are now being revealed in simple model systems in vertebrates such as the lamprey (Di Prisco et al., 1997).

The responsiveness of PPN neurones to somatosensory stimuli (Grunwerg et al., 1992; Reese et al., 1995), coupled with the cholinergic PPN projections to the thalamus (as described above) and the proposed inputs to the PPN from lamina I of the cat spinal cord (Hylden et al., 1985), suggests that the PPN may also take part in the modulation of sensory information to thalamic nuclei. The potential role of the PPN as a relay station, providing feedback information important for the modulation of posture and gait initiation, is facilitated by its prominent cholinergic ascending projections to the thalamus and its connections with deep cerebellar nuclei.

PPN neuronal activity during locomotion

Three separate populations of neurones displaying rhythmic activity in relation to locomotion can be recorded extracellularly in the area of the PPN in the decerebrate cat (Garcia-Rill and Skinner, 1988). One group of neurones displays a tonic firing pattern during locomotion which decreases in frequency or stops entirely with the cessation of the locomotor episode. These neurones have been termed ‘on’ cells. A second group of neurones, called ‘off’ cells, also display a tonic firing pattern, but their frequency decreases as the locomotion frequency increases and their firing rate increases before the cessation of locomotion. These two groups of neurones are located primarily within the PPN and may represent different subtypes of the previously defined cholinergic type II neurones (‘non-bursting’ neurones). The third group of neurones display a bursting pattern of firing during locomotion (termed ‘bursters’). These are located in more widespread areas and may represent the non-cholinergic type I neurones. The ‘on/off’ cells might modulate the duration of the stepping episode, while the bursters may be involved in modulating the frequency (and possible initiation) of stepping (Garcia-Rill and Skinner, 1991). Although their precise role remains to be defined, one can speculate that bursting, glutamatergic PPNd neurones, which are primarily innervated by GABAergic GPi (and possibly SNr) neurones and provide the main PPN outputs to the spinal cord, may be important for the initiation of programmed movements. In contrast, the non-bursting, possibly cholinergic PPNc neurones, which relay feedback sensory information from

...
the spinal cord and provide the main inputs back into the
thalamus and SNc, may be more important for the main-
tenance of gait.

Recently, the activity of PPN neurones was recorded in
awake cats (Dormont et al., 1998) and monkeys (Matsumura
et al., 1997) conditioned to perform lever-movement tasks.
In cats, the broad-spiked, low-frequency discharging neurones
(thought to be cholinergic) displayed increased activity,
especially during the programmed movements. In contrast,
the narrow-spiked, high-frequency discharging neurones
(thought to be non-cholinergic) displayed early activation
before the programmed movements (Dormont et al., 1998).
In monkeys, changes in PPN neuronal activity preceded the
onset of movement and occurred for both contralateral and
ipsilateral limb movements (Matsumura et al., 1997).

Regulation of gait and locomotion in the PPN
Continuous mid-frequency (20–60 Hz) stimulation in the cat
PPN is required to elicit locomotion. Hundreds of stimuli
delivered for several seconds must be applied before the first
step is induced (Garcia-Rill and Skinner, 1991). This effect
has been interpreted as one of ‘recruitment’ of locomotion, in
which spinal pattern-generators are activated by reticulospinal
systems triggered by stimulation of brainstem centres (Garcia-
Rill and Skinner, 1987b). Similarly, electrical stimulation of
the PPN in the rat (Kelland and Asdourian, 1989) and cat
(Lai and Siegel, 1990) has been reported either to reduce or
to stimulate muscle tone, depending on the rate of stimulation.
These results can be quite variable across laboratories because
differences in stimulation protocols (Garcia-Rill et al.,
1990). In contrast, high-frequency (>100 Hz) stimulation of
the cat PPN consistently induces suppression of muscle tone
(Lai and Siegel, 1990). It has been speculated that certain
stimulation parameters are necessary to shift PPN neurones
to a voltage ‘window’ conducive to increased locomotion
(Garcia-Rill et al., 1990). Mid-range frequencies may be
best, while higher frequencies appear to set the system into
a condition reminiscent of depolarization block.

The function of the PPN has also been inferred from
lesion and inhibitory neurotransmitter application studies.
Excitotoxic lesions (with kainic acid injections) of the monkey
PPN (as identified with extracellular recordings) produced
contralateral hemiparkinsonism characterized by flexed
posture and hypokinesia (Kojima et al., 1997). Radio-
frequency lesions in the PPN in rhesus monkeys reduced
motor activity significantly, as reflected by a generalized
bradykinesia that resembled Parkinson’s disease (Aziz et al.,
1998). Bilateral lesions were required to achieve long-
lasting effects. As outlined above, reversible pharmacological
inactivation of the monkey PPN with unilateral intracerebral
microinjections of lidocaine or a GABA agonist resulted in
delayed arrest of performance of a conditioned motor task
without motor impairment, suggesting an alteration in the
selection process of the appropriate motor programme (Condé
et al., 1998). Electrical stimulation at 50–60 Hz near the

PPN (Kölliker-Fuse nucleus) in a patient with chronic pain
produced increased tone in the contralateral limb muscles
(Young et al., 1992). There have been no other reports of
lesioning or stimulation of PPN areas in humans.

PPN, reward and motivation
The cholinergic PPN neurones may also provide a form of
non-specific facilitation for behaviours linked to the likelihood
of reward, so they may represent an interface between
limbic motivation systems and the brainstem motor apparatus
(Steckler et al., 1994). Cholinergic agonist stimulation of the
rat SNc (whose main cholinergic inputs may be provided by
PPNc neurones) increases the performance and initiation of
behaviours which the rat has pre-existing tendencies to
perform (Winn, 1991). Inhibition of cholinergic PPN neurones
with microinjections of carbachol can reduce the motor
performance elicited by amphetamine injected into the
nucleus accumbens (Brudzynski et al., 1988). In cats,
reinforcement-related activity in broad-spiked neurones
(thought to be cholinergic, as outlined above) is speculated
to be associated with the PPN cholinergic projection to the
SNc (Dormont et al., 1998). In contrast to Parkinson’s disease,
in human schizophrenic states, the number of cholinergic PPN
neurones is increased (Garcia-Rill et al., 1995; Yeomans,
1995). Since non-cholinergic neurones of the PPN receive
inputs from the basal ganglia and possibly the limbic
structures (as described above), it has been proposed that
the PPN, as a whole, also acts as an interface between
the selection of motor outputs by the basal ganglia and the
incentive-motivational directives from the striatal–pallidal
complex to provide motivationally influenced activation of
motor pattern generators in the pons, medulla and spinal cord
(Inglis and Winn, 1995). Such incentive-motivational or
affective factors may influence motor function, as occurs, for
example, in kinesia paradoxica. PPN activation could improve
motor planning, enabling an increased motivational ability to
call up already preserved motor programmes for stereotyped
movements such as locomotion and reaching.

The PPN and Parkinson’s disease
PPN neuropathology
It has been proposed that abnormalities of gait and posture,
in addition to rigidity and bradykinesia, may, in part, reflect
the loss of neurones or the suppression of neuronal activity
in the PPN. Analysis of the limited clinical data that are
available suggests a relationship between the loss of
cholinergic neurones in the PPNc and the severity of
Parkinson’s disease symptoms (Zweig et al., 1989). Thus,
the progression of Parkinson’s disease, and possibly the
change in response to levodopa (especially the refractory
akinesia) that can occur as the disease progresses in certain
patients, may reflect increasing involvement of non-
dopaminergic neuronal systems, such as the PPNC cholinergic and PPNd glutamatergic neuronal systems.

Neuropathological studies on humans have reported that ~50% of the large cholinergic neurones of the lateral part of the PPNC degenerate in Parkinson’s disease (Hirsch et al., 1987; Jellinger, 1988; Zweig et al., 1989; Gai et al., 1991). The extent of non-cholinergic neuronal loss in the PPN has not been determined. The observation that the magnitude of the neuronal loss within the PPNC is similar to the neuronal loss within the SNC raises the possibility that PPN neurones may be susceptible to the same pathogenetic mechanisms as nigral dopaminergic neurones. The PPN may also, at least in theory, have a role in SNC degeneration through an excitotoxic effect of glutamatergic synaptic contacts from the PPN onto dopaminergic SNC neurones (Lavoie and Parent, 1994c). This raises the intriguing possibility, for which there is so far no evidence, that reducing the glutamnergic drive from the PPN to the dopaminergic cells of the substantia nigra may have neuroprotective effects and influence the rate of progression of Parkinson’s disease.

PPN and the parkinsonian basal ganglia circuit model

In Parkinsonism, the inhibitory GABAergic projections from the GPI (and possibly the SNr) to the thalamus and PPN are overactive. Regional uptake studies of 2-deoxyglucose in MPTP-treated parkinsonian monkeys show increased synaptic activity in the PPN (Mitchell et al., 1989). It is not known, however, what effect this increased synaptic activity has on the net output of PPN neurones. Recent experiments using extracellular single-unit recordings from anaesthetized, 6-hydroxydopamine-lesioned rats have demonstrated decreased firing rates of PPN neurones in the parkinsonian state (Ogura et al., 1997), consistent with increased inhibition from basal ganglia outputs. An interesting hypothesis is that the increased GABAergic inhibition of PPN/locomotor region neurones from overactive descending pallidal (and possibly nigral) efferents in the parkinsonian state may underlie the problems of initiating programmed movements, the akinesia and the gait difficulties seen in parkinsonism. The pallidal–nigral projections appear to terminate preferentially on the non-cholinergic, glutamatergic neurones of the PPNd and largely avoid neurones of the PPNC (Shink et al., 1997), and these glutamatergic PPNd neurones provide descending projections to the spinal cord. Furthermore, reducing PPN activity, as occurs with destructive lesions, leads to a parkinsonian-like state (Kojima et al., 1997; Aziz et al., 1998). Medical or surgical intervention that reduces the overactive inhibitory outflow from the basal ganglia to PPN would be expected to release the activity of this nucleus and facilitate a return towards normal function.

Potential surgery and the PPN in parkinsonism

There is already good evidence from animal and clinical studies that surgical interventions which are designed to reduce the inhibitory basal ganglia output to the thalamus and PPN are associated with striking improvements in all major features of parkinsonism. Lesions of the STN in normal monkeys decrease the neuronal activity of inhibitory GPi projections to the thalamus and PPN (Mitchell et al., 1989). STN lesions and chronic electrical stimulation in parkinsonian monkeys and patients with Parkinson’s disease reduce all the major motor disturbances of Parkinson’s disease, including akinesia, rigidity and tremor (Bergman et al., 1990; Aziz et al., 1991, 1992; Benazzouz et al., 1993; Benabid et al., 1994; Limousin et al., 1995, 1998; Pollak et al., 1996; Gill and Heywood, 1997; Kumar et al., 1998a, b). Direct lesioning or stimulation of the GPi in human and non-human primates also improves parkinsonism (Gross et al., 1997, 1999; Lang et al., 1997; Galvez-Jimenez et al., 1998; Krack et al., 1998; Volkmann et al., 1998; Lieberman et al., 1999). These observations are consistent with the hypothesis that the overactive inhibitory influence from the basal ganglia to the PPN is important in the pathogenesis of motor dysfunction in parkinsonism and that removing this disruptive influence on PPN improves motor function.

Would surgical procedures of the PPN be of therapeutic value? The experimental data show that both electrical stimulation and the delivery of neuroactive substances in their PPN have striking effects on motor function. It may be possible to place a chronic deep brain stimulation electrode or a microinfusion cannula for the delivery of neuroactive substances directly into the PPN to change its activity and modulate its output to its targets. The direct infusion of neuroactive substances into the PPN, as has been described recently in the globus pallidus and thalamus of patients (Penn et al., 1998; Pahapill et al., 1999), opens a number of new possibilities. Experiments in parkinsonian animals are needed to address some of these issues.

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