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Review

Reciprocal interaction between monoaminergic systems and the pedunculopontine nucleus: Implication in the mechanism of L-DOPA

Giuseppe Di Giovanni[a,b,*], Abdeslam Chagraoui[c,f], Emilie Puginier[c,f], Salvatore Galati[d], Philippe De Deurwaerdère[e,**]

[a] Department of Physiology & Biochemistry, Faculty of Medicine and Surgery, University of Malta, Msida, Malta
[b] Neuroscience Division, School of Biosciences, Cardiff University, Cardiff, UK
[c] Normandie Univ, UNIROUEN, INSERM, U1239, CHU Rouen, Neuronal and Neuroendocrine Differentiation and Communication Laboratory, Institute for Research and Innovation in Biomedicine of Normandy (IRIB), Rouen, France
[d] Parkinson and movement Disorders Center Neurocenter of Southern Switzerland, Ospedale Civico di Lugano, Lugano, Switzerland
[e] Centre National de la Recherche Scientifique (Unité Mixte de Recherche 5287), 146 rue Léo Saignat, B.P.281, F-33000 Bordeaux Cedex, France
[f] Department of Medical Biochemistry, Rouen University Hospital, Rouen, France

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ABSTRACT

The pedunculopontine nucleus (PPN) is part of the mesencephalic locomotor region (MLR) and has been involved in the control of gait, posture, locomotion, sleep, and arousal. It likely participates in some motor and non-motor symptoms of Parkinson's disease and is regularly proposed as a surgical target to ameliorate gait, posture and sleep disorders in Parkinsonian patients. The PPN overlaps with the monoaminergic systems including dopamine, serotonin and noradrenaline in the modulation of the above-mentioned functions. All these systems are involved in Parkinson's disease and the mechanism of the anti-Parkinsonian agents, mostly L-DOPA. This suggests that PPN interacts with monoaminergic neurons and vice versa. Some evidence indicates that the PPN sends cholinergic, glutamatergic and even gabaergic inputs to mesencephalic dopaminergic cells, with the data regarding serotonergic or noradrenergic cells being less well known. Similarly, the control exerted by the PPN on dopaminergic neurons, is multiple and complex, and more extensively explored than the other monoaminergic systems. The data on the influence of monoaminergic systems on PPN neuron activity are rather scarce. While there is evidence that the PPN influences the therapeutic response of L-DOPA, it is still difficult to discerne the reciprocal action of the PPN and monoaminergic systems in this action. Additional data are required to better understand the functional organization of monoaminergic inputs to the MLR including the PPN to get a clearer picture of their interaction.

1. Introduction

The pedunculopontine nucleus (PPN) is part of the mesencephalic locomotor region (MLR), a large area composed of several nuclei and involved in the initiation and the pattern of locomotion as well as posture (Ryczko & Dubuc, 2013; Shik et al., 1966; Takakusaki et al., 2016). The PPN itself is a heterogeneous nucleus in terms of anatomofunctional influences and neurochemical markers. Human data

Abbreviations: 6-OHDA, 6-hydroxydopamine; 5-HT, 5-hydroxytryptamine (serotonin); AADC, aromatic L-amino acid decarboxylase; Ach, Acetylcholine; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; CnF, cuneiform nuclei; CNQX, 6-cyano-7-nitroquinoxaline-2,3-dione; CNS, Central Nervous System; CSF, Cerebrospinal fluid; DA, dopamine; DAG, di-acylglycerol; DAT, DA transporter; DRN, dorsal raphe nucleus; EEG, electroencephalogram; fMRI, functional magnetic resonance imaging; GABA, gamma-aminobutyric acid; GAD GPi, internal segment of the globus pallidus; L-DOPA, L-3,4-dihydroxyphenylalanine; LC, locus coeruleus; LDT, laterodorsal tegmental nucleus; LFP, local field potential; LH, lateral hypothalamus; LTS, low-threshold spike; MLR, mesencephalic locomotor region MPTP, 1-methyl-4-phenyl-1,2,3,6-tetra hydropyridin; MRN, median raphe nucleus; NA, noradrenaline; NET, noradrenergic transporters; NMDA, *N*-methyl-D-aspartate; NOS, nitric oxide synthase; PD, Parkinson's disease; PPN, pedunculopontine nucleus; RAS, reticular activating system; REM, rapid eye-movement; RN, raphe nucleus; SERT, serotonin transporter; SNc, substantia nigra pars compacta; SNr, substantia nigra pars reticulata; STN, subthalamic nucleus; SWS, slow wave sleep; TH, tyrosine hydroxylase; VMAT2, vesicular monoamine transporter 2; VTA, ventral tegmental area; W, waking

* Corresponding author at: Laboratory of Neurophysiology, Department of Physiology & Biochemistry, Faculty of Medicine and Surgery, University of Malta, Msida, Malta.
** Corresponding author.
E-mail addresses: giuseppe.digiovanni@um.edu.mt (G. Di Giovanni), philippe.de-deurwaerdere@u-bordeaux.fr (P. De Deurwaerdère).

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recently reported that the PPN could correspond to a functional node between some cortical areas and the brainstem nuclei and witnessed the functional heterogeneity of the nucleus. The interest brought on the PPN is gaining notably in central nervous system (CNS) diseases associated with arousal, gait, sleep, locomotor function (Caggiano et al., 2018; Garcia-Rill, 2017; Josset et al., 2018). As a matter of fact, the PPN has been a candidate region for deep brain stimulation (DBS) in Parkinson's disease (PD) for several years (French & Muthusamy, 2018; Mazzone et al., 2014; Stefani et al., 2007).

Monoaminergic systems, including serotonin (5-HT), dopamine (DA) and noradrenaline, are diffuse in the brain (De Deurwaerdere et al., 2017b). On one hand, these systems innervate the PPN and participate in similar functions including arousal, sleep, gait and more generally locomotion. It is noteworthy that the PPN (and its medial partner, the laterodorsal tegmental nucleus), the locus coeruleus (LC, mainly noradrenergic) and the raphe nuclei (RN, containing serotonergic cell bodies) constitute regional elements of the reticular activating system (RAS) (Brown et al., 2012). On the other hand, the PPN sends projections to dopaminergic, serotonergic and noradrenergic centres. Reciprocal interaction has been proposed but it is still unclear how these different systems interact, in particular when monoamine-based medications are administered.

The purpose of this short analysis is to present the reciprocal link between monoamines and the PPN in term of anatomy, activity, and function. Thereafter, we will discuss this reciprocity in the mechanism of action of the anti-Parkinsonian treatment L-DOPA.

2. Reciprocal anatomical contacts between PPN and monoaminergic centres

Anatomically, the pedunculopontine nucleus (PPN) is a wedge-shaped cell group extending from the dorsolateral to the ventrolateral mesopontine region, just at the level of the red nucleus and dorsal to the substantia nigra. It is laterally bordered by the medial lemniscus and medially by fibres of the superior cerebellar peduncle. The cytoarchitecture of the human PPN exhibits two distinct regions: a pars dissipata (PPNd), located throughout the rostrocaudal extent of the nucleus and composed of small and medium-sized cells, and a pars compacta (PPNc), present in the caudal half of the nucleus and composed of densely distributed neurons (Mesulam et al., 1989; Pahapill & Lozano, 2000). This region contains neurons synthetizing acetylcholine, gamma-aminobutyric acid (GABA), or L-glutamate (Fig. 1).

The efferent neurons can contact the noradrenergic neurons in the LC, serotonergic neurons of the RN including the dorsal raphe nucleus (DRN) and dopaminergic neurons of the substantia nigra pars compacta (SNc) as discussed below.

2.1. Heterogeneous contacts from the PPN on monoaminergic cells

Using acetylcholinesterase labelling methods two pathways that were originally described as originate from the midbrain reticular formation ascending toward the thalamus and basal forebrain (Wang & Morales, 2009) have been identified. In later investigations using choline acetyltransferase (ChAT) immunolabelling, the source of these projections has been identified as cholinergic neurons in the posterior midbrain located in the PPN and the laterodorsal tegmental nucleus (LDT) nuclei (Mesulam et al., 1983). These ascending inputs from the PPN path dorsally toward the intralaminar thalamus and most medial thalamic nuclei, while ventral projections path toward the SNc, lateral hypothalamus, subthalamic region and the basal forebrain. The dorsal projection system also ends in each thalamic nucleus (Steriade & McCarley, 2005).

In situ hybridization labelling studies and immunohistochemistry have demonstrated that the PPN contains distinct neuronal populations of glutamatergic, GABAergic, apart from cholinergic cells (Wang & Morales, 2009). Coexpression of markers for glutamate and GABA with markers for ACh implies that the cholinergic PPN neurons may also release glutamate and GABA (Lavoie & Parent, 1994).

Both cholinergic and glutamatergic neurons contact nigral neurons (Lavoie & Parent, 1994). It has been also shown that nigral DA neurons receive glutamatergic and possibly GABAergic inputs from the PPN (Charara et al., 1996).

2.2. Projection of monoamines on PPN neurons

2.2.1. Dopaminergic innervation

Mesencephalic dopaminergic neurons located in the SNc and the ventral tegmental area (VTA) project to the striatum, the nucleus accumbens or the cortex (Bjorklund & Dunnett, 2007; Björklund & Lindvall, 1986). The degeneration of the dopaminergic pathway originating in the SNc and innervating the putamen (dorsal striatum) is considered as the pathophysiological hallmark of PD. Yet, in line with previous evidence that PPN contained DA and dopaminergic fibres, some dopaminergic SNc neurons are innervating PPN. It has been originally determined in lamprey, a basal vertebrate. In an elegant study, the authors provided anatomical evidence for the existence of this pathway with neurons contacting both the striatum and the MLR. They further showed that nigral stimulation enhanced DA release in the PPN in lamprey (Ryczko et al., 2013). Moreover, they described the pathway in other species such as salamander and mammals including rodents, monkeys and humans (Ryczko et al., 2016). These findings likely explain the fact that the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetra hydropyridine (MPTP), known to destroy dopaminergic neurons of the SNc and used in monkeys as the gold standard model of PD, reduced DA fibres in the PPN of monkeys (Rolland et al., 2009). These results are also compatible with the anatomical description of nigrotegmental projection in the rat (Grofova & Zhou, 1998) although the latter can be related to the indirect influence of the DA systems on PPN. In addition, a glutamatergic pathway from the SNc and innervating the MLR has been recently described in lamprey (Ryczko et al., 2017).

The relationship between the PPN and the basal ganglia has been studied for several years, the PPN often appearing in the anatomo-functional models of the basal ganglia (Mena-Segovia & Bolam, 2017; Redgrave et al., 2011). Because DA plays a central role in the functional architecture of the basal ganglia, we recall here the indirect anatomical contact from mesencephalic dopaminergic neurons to the PPN. Indeed, the PPN established numerous mutual connections with the output structures of the basal ganglia, the subthalamic nucleus or the striatum (Mena-Segovia & Bolam, 2017).

The distribution of DA receptors has been the object of numerous studies in the past and it is known for several brain regions (Missale et al., 1998). However, it has not been the object of specific studies in the MLR and we cannot indicate whether PPN and surrounding areas express DA receptors.

2.2.2. Noradrenergic innervation

Noradrenergic neurons of the LC are quite segregated from PPN neurons but overlapping has been also reported (Lavoie & Parent, 1994). In the PPN, cells became fewer medially and are intertwined with neurons of the LC. LC neurons, although dispersed are evident among lateral LDT neurons. α2 adrenergic receptor development is recognized to undergo significant changes in the LC as well as in other mesopontine areas from 15 days of age in the rat (Happe et al., 2004). Interestingly, approximately half of the α2 adrenergic receptor immunocytochemical labelling, was found in adult cholinergic mesopontine neurons, versus a third of α1 adrenergic receptor labelling (Happe et al., 2004). It is noteworthy that specific projections from the LC to the PPN are usually not evoked in articles addressing neuroanatomical (Caggiano et al., 2018; Edley & Graybiel, 1983; Jackson & Crossman, 1983) or functional connectivity in rodent, monkey and human brain (Aravamuthan et al., 2008b; Muthusamy et al., 2007). As described in squirrel monkeys, dendrites of noradrenergic and

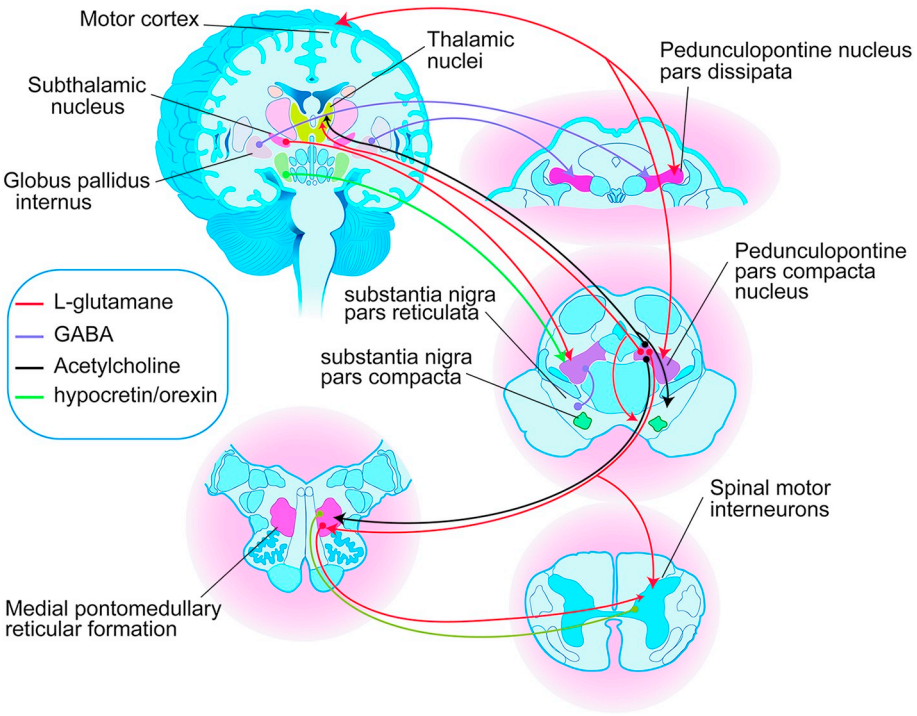

Fig. 1. The cytoarchitecture of the human PPN exhibits two distinct regions: a pars dissipata (PPNd), located throughout the rostrocaudal extent of the nucleus and composed of small and medium-sized cells, and a pars compacta (PPNc), present in the caudal half of the nucleus and composed of densely distributed neurons (Mesulam et al., 1989; Pahapill & Lozano, 2000) and contains neurons synthetizing acetylcholine, gamma-aminobutyric acid (GABA), or L-glutamate. The motor cortex and the globus pallidus internus (GPi) and substantia nigra pars reticulata (SNr), as well as the subthalamic nucleus (STN) and deep cerebellar nuclei send direct glutamatergic projections to the PPN. Both cholinergic and noncholinergic neurons of the PPN provide ascending and descending inputs. The primary target of ascending projections is the GPi, substantia nigra pars compacta (SNc), and the intralaminar and associative nuclei of the thalamus. Descending projections reach directly the pontine and medullary reticular formation and the spinal cord and are involved in the control of muscle tone and locomotion.

cholinergic neurons in the PPN are closely intermingled and this could be the main, direct way of interaction between the two systems in this region (Lavoie & Parent, 1994).

2.2.3. Serotonergic innervation

Several studies have shown the presence of 5-HT in the MLR and ultimately in the PPN. An ultrastructural study reported the existence of serotonin terminals contacting or not cholinergic neurons of the PPN and LDT (Honda & Semba, 1994). The authors reported also different shapes of 5-HT terminals which could be due to different origin of 5-HT fibres. Using retro and anterograde tracers in rats, it has been shown that the DRN, the MRN and the raphe magnus (B5) contact the PPN (Semba & Fibiger, 1992). The presence of 5-HT fibres corresponds also to the presence of serotonin transporters (SERT) (De Souza & Kuyatt, 1987).

Numerous 5-HT receptors are thought to be expressed by PPN neurons or present in the dorsal tegmentum via afferent projections but their level of expression appears to be moderate to low. In most cases, it is not explicitly mentioned in the anatomical studies. Using a 5-HT_{1A} receptor antibody, it has been reported moderate levels of 5-HT_{1A} receptors in the PPN/LDT (Kia et al., 1996). This result is consistent with the distribution of the mRNA and binding sites labelled with ^{3}H-8-OHDPAT (Pompeiano et al., 1992). The 5-HT_{1B} receptor is usually expressed in higher density than the 5-HT_{1A} receptor in mesencephalic/pontic regions with the exception of raphe nuclei (Pazos & Palacios, 1985; Pazos et al., 1987; Sari et al., 1997). Immunohistochemical studies have reported that 5-HT_{2A} receptors are present in the MLR including the cuneiform nuclei, PPN and subcoeruleus nucleus although the labelling was found dense in a first study and loosely scattered in a second one (Fay & Kubin, 2000; Morilak & Ciaranello, 1993). Labelled cells were reported in the rat caudal PPN and LDT. Labelling did not colocalize with NOS, a marker of cholinergic neurons in this structure (Fay & Kubin, 2001) although they did with choline acetyltransferase (Morilak & Ciaranello, 1993). Rather, the 5-HT_{2A} receptor-labelled cells, smaller in size and number, could correspond to interneurons (Fay & Kubin, 2001). The autoradiographic studies using radiolabelled ligands usually report a low level of 5-HT_{2A} receptor binding (Pazos & Palacios, 1985). The 5-HT_{2C} receptors are present in the brainstem and likely expressed by neurons of the PPN/LDT (Clemett et al., 2000). However, their expression is quite low relative to other brain areas (Mengod et al., 1990; Pazos & Palacios, 1985; Pazos et al., 1987). The distribution of 5-HT_3 receptors (either 5-HT_{3A} or 5-HT_{3B} subunits) is unclear as regards the MLR (Doucet et al., 2000; Doucet et al., 2007; Morales & Wang, 2002). The expression of 5-HT_4 receptors with a specific mention to MLR is unknown. It is noteworthy that these receptors are present in high density in the substantia nigra par reticulata (SNr) and the globus pallidus and the striatum (Domenech et al., 1997; Reynolds et al., 1995). The levels of 5-HT_6 receptors as revealed by immunostaining and RT-PCR is moderate to low in areas corresponding to the MLR with respect to other brain regions such as the hippocampus, cerebellum, basal ganglia or spinal cord (Gerard et al., 1996; Gerard et al., 1997). This has been confirmed using the radioligand (125)I]SB-258585 (Roberts et al., 2002). 5-HT_7 receptor mRNA and binding sites are present in some pontic nuclei without specific reference to the MLR (Gustafson et al., 1996). Like the catecholaminergic receptors, the analysis of the available evidence is scarce for serotonergic receptors. The consequence is that it is impossible to determine the neuronal type expressing monoamine receptors (except for 5-HT_{2A} receptors but the data are controversial) and distinct density with respect to a rostrocaudal distribution of these receptors has not been reported.

3. Reciprocal influences between PPN and monoaminergic centres

3.1. Heterogeneous influences from PPN toward monoaminergic cells activity

Both cholinergic and glutamatergic influence on monoaminergic neurons has been reported. The stimulation of PPN increases the firing rate of SNc neurons (Di Loreto et al., 1992) and, using iontophoretic approach, it has been described that glutamatergic, non-NMDA receptors, were involved in such an excitation (Di Loreto et al., 1992). Very recently, it has been reported that PPN neurons can promote burst activity in DA neurons of the SNc, likely due to contact at proximal dendrites of SNc neurons. The change of pattern from tonic to burst mode was initiated by AMPAs receptors (Galtieri et al., 2017).

Nonetheless, NMDA receptors could also be involved in the ability of the PPN to enhance DA neuron activity. Unilateral lesion of the PPN is associated with a decrease in spontaneously active DA neurons and no modification of their firing rate in the SNc of the ipsilateral side. The PPN lesion was associated with an increase in STN and SNr neuron activity (Breit et al., 2005).

The excitatory influence of the PPN on DA SNc neurons is not only glutamatergic as exemplified previously (Futami et al., 1995). Remaining excitatory post-synaptic potentials evoked by PPN stimulation in vitro on DA SNc neurons persisted in the presence of saturating concentration of kynurenic acid and CNQX to block NMDA and AMPA receptors respectively. The remaining effect was reduced by anti-cholinergic agents blocking muscarinic and nicotinic receptors (Futami et al., 1995). Gronier and Rasmussen (1998) showed that microiontophoretic application of muscarinic agonists increased the firing rate of both VTA and SNc DA neurons, but had no effect on burst firing of SNc DA neurons. Nevertheless, no significant tonic influence of muscarinic receptors on spontaneously active SNc DA neuron seems to be present in nature. Indeed, blockade of muscarinic receptors by intraperitoneal administration or microiontophoretic application of scopolamine, did not produce a discernible effect on firing rate or pattern of SNc neurons (Hand et al., 1987; Di Giovanni & Shi, 2009), but increased the number of spontaneously active DA neurons when was both given i.p. or into the PPN. Therefore, it might be possible that scopolamine by blocking the inhibitory muscarinic autoreceptors in the PPN preferentially excites quiescent DA neurons in the SNc (Di Giovanni & Shi, 2009), thereby contributing to the scopolamine-induced increase in DA release in the striatum (Chapman et al., 1997).

Stimulation of the PPN or LDT has also been shown to alter DA extracellular levels in the striatum or the nucleus accumbens in a complex manner, respectively (Forster & Blaha, 2000; Forster & Blaha, 2003). The mechanism described is similar in both cases with a triphasic response characterized by a short excitation followed by an inhibition and a later and longer excitation. Using intracerebral injections into the SNc or the VTA, the authors identified glutamatergic and nicotinic effects in the first excitatory response and a muscarinic component in the late excitatory response. The inhibition was attributed to M2 autoreceptors in the pontine regions reducing the impact of the stimulation. The authors propose the involvement of different muscarinic receptors including M3 and M5 in mediating the complex effects of acetylcholine in the regulation of DA neuron activity (Lester et al., 2010).

Finally, the regulatory role of cholinergic input from the PPN/LDT on DA neurons is likely more complex. It has been recently reported that the stimulation of cholinergic afferences from both PPN and LDT excited VTA DA neurons activity. However, the circuits were distinct as PPN stimulation altered the activity of DA neurons that were inhibited by aversive stimulus whereas LDT stimulation altered the activity of DA neurons that were excited by aversive stimuli (Dautan et al., 2016).

Microiontophoretic application of acetylcholine has been shown to enhance the activity of LC neurons (Bird & Kuhar, 1977). The excitatory cholinergic input from the PPN interacts with LC neurons through nicotinic and muscarinic M2 receptors (Egan & North, 1985; Egan & North, 1986).

Once released from the PPN, ACh stimulates DRN neurons via nicotinic receptors (Monckton & McCormick, 2002).

3.2. Multiple influences of monoamines on PPN neuron activity

Electrophysiologically, three types of PPN neurons can be distinguished on the basis of intrinsic membrane properties (Kayama et al., 1992; Kobayashi et al., 2003; Steriade et al., 1990).

Several sources can modulate the activity of these neurons. The release of glutamate from glutamatergic inputs, originating mainly from the cerebral cortex, increases cholinergic PPN neurons firing through NMDA receptors (Sanchez & Leonard, 1994). The release of acetylcholine from cholinergic inputs originating from the LDTg and contralateral PPN elicits somatodendritic inhibition of the PPN neurons through M2 and M4 receptors (Leonard & Llinas, 1994) and inhibits glutamate or GABA release in the PPN through presynaptic M2 receptors (Ye et al., 2010). The release of GABA from GABAergic inputs originating from the internal segment of the globus pallidus (GPi)/SNr and other sources causes postsynaptic inhibition in both cholinergic and noncholinergic neurons (Kang & Kitai, 1990). In contrast, histamine and hypocretin/orexin activate respectively H1 (Khateb et al., 1990) and orexin 1 receptors to increase excitability of these cells (Kim et al., 2009).

Like the anatomy, the influence of monoamines on PPN/LDT activity is unclear and would deserve additional studies. Very few data have reported a direct action of DA or DA receptors on the activity of PPN. It has been shown that local application of DA or the D1 receptor antagonist SCH23390 enhanced and reduced the activity of neurons located in the MLR of the lamprey, respectively (Ryczko et al., 2013). In most cases, the data concerning DA and dopaminergic agents are interpreted as the indirect consequences of the changes in dopaminergic transmission within the basal ganglia, thereby leading to alter the activity of PPN/LDT neurons via output structures of the basal ganglia (Monti & Monti, 2007).

It has been reported that clonidine (known as α2 adrenergic receptor agonist) was capable of reducing or blocking the hyperpolarization-activated inward cation conductance on a given population of PPN neurons (Bay et al., 2006). NA has an inhibitory effect on cholinergic PPN neurons via α-2 adrenergic receptors, while it has an excitatory effect on noncholinergic PPN neurons (Kohlmeier & Reiner, 1999; Williams & Reiner, 1993) (Miyazato et al., 2000b; Pal & Mallick, 2006). NA has also been found to hyperpolarize 7–15 day cholinergic mesopontine neurons in the LDT during the developmental decrease in rapid-eye-movement (REM) sleep (Williams & Reiner, 1993).

Serotonin exerts complex effects on the activity of PPN neurons. It has an inhibitory influence through 5-HT_{1A} receptors (Grace et al., 2012) and, in general, the stimulation of 5-HT_1 receptors with agonists including 5-HT reduces the neuronal activity of PPN neurons and hyperpolarizes neurons (Kobayashi et al., 2003; Koyama & Kayama, 1993). The effect of 5-HT evolves during development. Inhibitory responses to the serotonergic agonist 5-carboxytryptamin are found together with no response and excitatory responses of PPN neurons before P17 and become the main response (85%) after P21 (Kobayashi et al., 2003).

4. Functional interplay of monoamines and PPN in sleep wake cycle

The PPN shows the higher activity during waking and REM sleep and contributes directly to generating the activated states of waking and REM sleep and to lowering slow wave sleep (SWS) (Garcia-Rill, 2017; Steriade et al., 1990) (Deurveilher & Hennevin, 2001; Shouse & Siegel, 1992). Serotonergic and noradrenergic neurons located near the PPN (Leonard et al., 1995) are believed to be the “wake-on” neurons in the cat (Kayama et al., 1992). As reported above, neither serotonergic nor adrenergic neurons are present in the PPN of the rat (Wang & Morales, 2009). Only “REM-on” and “wake - REM-on” neurons and no “wake-on” neurons (Datta & Siwek, 2002) appear to be present (Datta & Siwek, 2002).

The LC receives serotonergic afferents from the DRN (Pickel et al., 1977) and excitatory orexigenic projections from the lateral hypothalamus (Hagan et al., 1999). Microdialysis studies have shown a decrease of GABA release into the LC during waking but an increase during SWS, and highest level during REM sleep. No changes were noted in the levels of glycine and glutamate release (Nitz & Siegel, 1997b). These findings suggest that GABA release in the LC is greater during REM sleep, which explains that the activity of LC neurons turns off during REM sleep ((Nitz & Siegel, 1997b). During waking, the LC is

active. This can be attributed in part to stimulation by cholinergic and orexigenic afferents, leading to an increase of NE, and stimulation of the cerebral cortex. During SWS, the release of NE is decreased in part due to excitatory input decreases and inhibitory input increases. Moreover, LC neurons as a result of the diminishing of excitatory and increasing GABAergic inhibitory drive (Mahaffey & Garcia-Rill, 2015).

The LC sends noradrenergic projections to the DRN, which exerts an excitatory effect via the α-1 adrenergic receptors (Dodt et al., 1991). Orexin and histamine also exert an excitatory effect on DRN neurons (Dodt et al., 1991). DRN neurons contain 5-HT_{1A} autoreceptors which exert a negative feedback on 5-HT release (Bjorvatn et al., 1997). DRN displayed elevated GABA release during REM sleep but no changes in glycine or glutamate release (Nitz & Siegel, 1997a). A 5-HT_{1A} receptor appears to inhibit REM-on" neurons in the PPN but had a negligible effect on "wake/REM-on" neurons (Thakkar et al., 1998). The injection of 8-OHDPAT into the PPN has been shown, via a 5-HT_{1A} receptor-dependent mechanism to reduce the amplitude of the sleep state-dependent P13 midlatency auditory evoked potential in the rat (Miyazato et al., 2000a).

There is evidence supporting a role of DA neurons in mediating reward functions, locomotor activity and cognitive functions in the midbrain (Le Moal & Simon, 1991; Schultz, 1998). Interestingly, one study indicated that burst firing may be linked to the emergence of waking EEG (Rye & Jankovic, 2002). In the midbrain, the dopaminergic cells would change the temporal pattern rather than the firing rate during the sleep-wake state. Burst firing of dopaminergic neurons would depend on projections from the prefrontal cortex (Lokwan et al., 1999; Overton & Clark, 1997). Furthermore, projections from the LC and the DRN have also been suggested to facilitate the emergence of bursting activity (White, 1996). Considering that activation of the PPT/LDT nuclei, the LC, the DRN or the lateral hypothalamus, evokes W from sleep and produces and preserves W, it has been proposed that their initiation of burst firing and the consecutive increase in DA release contribute to the emergence of W (Monti & Monti, 2007).

5. PPN status in Parkinson's disease

The progressive degeneration of the dopaminergic neurons in SNc and non-DA neurons particularly, cholinergic neurons of the PPN (Hirsch et al., 1988), leading to dysfunction of the basal ganglia system and the emergence of typical motor symptoms of PD is preceded by a pre-symptomatic stage characterized by non-motor features affecting sleep, mood and autonomic function (Goldman & Postuma, 2014; Wolters & Braak, 2006). Previous studies provided evidence that a significant PPN lesion was associated with Parkinsonian syndrome in primates (Aziz et al., 1998; Kojima et al., 1997; Matsumura & Kojima, 2001). Furthermore, excitotoxic damage of the PPN was reported to cause nigral cell death in rodent (Gonzalez-Hernandez et al., 1997; McGeer & McGeer, 1984). Unilaterally lesioned PPN produced oxidative stress events in both the striatum and SNc (Blanco-Lezcano et al., 2017; Jimenez-Martin et al., 2015). These findings raise the possibility that pontine-nigral projections might be involved in the survival of dopaminergic neurons in the adult brain and this effect might diminish until disappearing in PD (Michel et al., 2013). The reciprocal modulation of functions between nigral dopaminergic neurons and cholinergic/glutamatergic pontine neurons (Fig. 2A-B), makes them mutually dependent to promote homeostasis and maintenance of survival (Bensaid et al., 2016). In line with this evidence, it has been recently shown that the PPN lesion increases tyrosine hydroxylase (TH) mRNA expression with a parallel decrease of the vesicular monoamine transporter 2 (VMAT2) and the DA transporter (DAT) in nigrostriatal tissue of rats (Blanco-Lezcano et al., 2018).

Excessive DA release becomes neurotoxic since DA is highly reactive and can be oxidized to form reactive oxygen species and reactive quinones through its cytosolic metabolism ((Graham, 1978); LaVoie and (Hastings, 1999; Meiser et al., 2013)). The sequestration of DA in vesicles enables the reduction and prevention of neurotoxic effects of the endogenous DA by limiting the oxidation processes (Caudle et al., 2008; Taylor et al., 2011; Wimalasena, 2011). Thus, loss of the nigrostriatal redox balance induced by the neurotoxic lesion of the PPN may lead to alterations in mRNA expression of several proteins involved in nigrostriatal dopaminergic homeostasis.

The post-mortem tissues analysis from the patients with advanced PD revealed neuronal degeneration in the PPN which is correlated with the degree of DA depletion and the severity of pre-mortal gait dysfunction (Hirsch et al., 1987; Jellinger, 1988; Pahapill & Lozano, 2000). Indeed, freezing of gait and postural instability appear always more unresponsive to dopaminergic drugs during the disease course (Jankovic et al., 1990) suggesting an extra-striatal pathophysiological mechanism of intractable axial symptoms (Chung et al., 2010). In accordance, decreased thalamic cholinergic input form PPN measured by brain PET imaging is associated with fall in patients with PD (Bohnen et al., 2009). In normal monkeys, neurotoxin lesioning of the cholinergic neurons of the PPN induced gait and postural abnormalities (Karachi et al., 2010). However, recent findings in rats demonstrated that only the combined dopaminergic and cholinergic lesion is needed for the freezing of gait (Xiao et al., 2017). However, the role played by PPN in locomotion could be not strictly acetylcholine-mediated. In mice speed and gait selection are controlled by glutamatergic neurons of both the cuneiform nucleus and the PPN (Caggiano et al., 2018).

In PD, hyperactivation of pallidal and nigral inhibitory inputs to the PPN may result in the sequential apparition of PPN hypofunction (Fig. 2B), diminished excitatory synaptic input to the substantia nigra, and contributed substantially to the striatal DA deficiency. In MPTP-lesioned primates, 2-deoxyglucose activity was markedly elevated in the PPN, most probably as a result of overactive inhibitory pallidal inputs (Crossman et al., 1987; Palombo et al., 1990). These observations suggest that increased pallidal inhibition to PPN may exacerbate striatal DA deficiency in PD. Although the approach of overexciting PPN neurons with kainic acid injection into the PPN induces damage to the SN dopaminergic neurons (McGeer & McGeer, 1984), there is no evidence that hypoactive PPN in patients with parkinsonism slows down the progressive decline of neuronal loss in the SNc. Of note, chronic DA-depleted animals show abnormal connectivity in the theta and alpha range between cortex and PPN during cortical activation (Valencia et al., 2014) (Fig. 2B).

6. PPN and monoaminergic systems in L-DOPA's effects in Parkinson's disease

L-DOPA is considered as one of the best available medication in PD (Mercuri & Bernardi, 2005; Rajput et al., 2004). Numerous side effects have been described with L-3,4-dihydroxyphenylalanine (L-DOPA) therapy (Bastide et al., 2015). Treatment with L-DOPA is associated in some patients with sleep disorders, postural instability, gait disorder and fluctuation. The various effects and side-effects evoked by L-DOPA in clinic likely overwhelm the putaminal DA transmission (Rochester et al., 2011). For Rycko and Dubuc (Ryczko & Dubuc, 2017) the action of L-DOPA on some gait parameters, posture or fluctuation in clinic (Bryant et al., 2011; Bryant et al., 2016; Moore et al., 2008; Rochester et al., 2011) could be related to the release of DA in the MLR (Ryczko & Dubuc, 2017). With specific inference to the topic of the review, poor locomotor responses to L-DOPA could be associated to MLR degeneration (Chastan et al., 2009; Karachi et al., 2010; Snijders et al., 2011). Moreover, noradrenergic or serotonergic systems are altered at various degrees across the course of the disease, sometimes earlier and more severely than DA neurons in the case of NA neurons (Braak et al., 2002; Delaville et al., 2011; Eskow Jaunarajs et al., 2011; Galati & Di Giovanni, 2010; Jenner et al., 1983; Kish et al., 2008; Qamhawi et al., 2015). Neuroimaging studies in humans suggest that serotonergic disturbances in PD (Politis et al., 2010) could be associated with sleep disorders (Wilson et al., 2018) whereas others suggest a link with

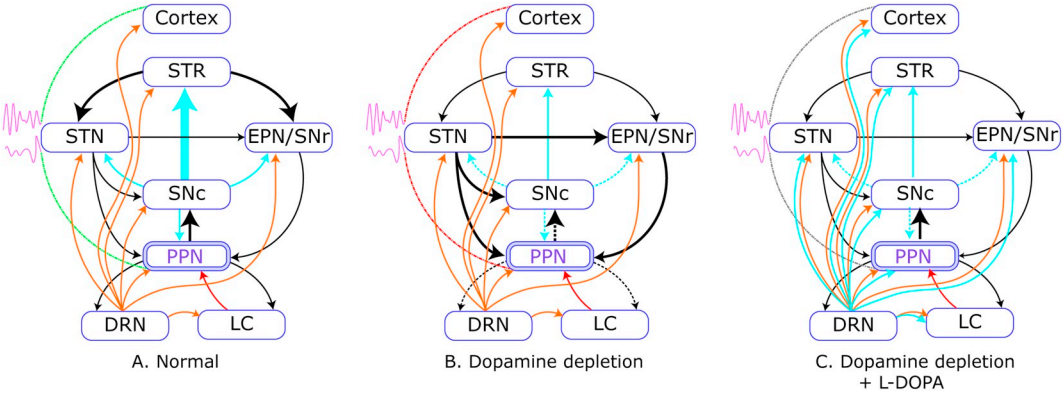

Fig. 2. Interaction between monoamines and the PPN in different situations related to Parkinson's disease (PD). The three panels display the cortex, the entry (subthalamic nucleus, STN, striatum, STR) and the outputs (entopeducular nucleus, EPN and substantia nigra pars reticulata, SNr) structures of the basal ganglia, the PPN and the brain regions containing dopaminergic neurons (substantia nigra pars compacta, SNc; blue), serotonergic neurons (dorsal raphe nucleus, DRN; orange) and noradrenergic neurons (Locus coeruleus, LC; red). Noradrenergic neurons are, almost like serotonergic neurons, widespread in the brain (voluntary kept minimal in the schemas). These brain regions interact either directly or indirectly and we report here only connections from known anatomofunctional models that are pertinent for our purpose. The physical connections and their strength can vary according to the situation (size and nature of the line, the uniformed dashed line symbolizing low influence). In addition, we have simply reported the existence of a functional connectivity in theta/alpha band between the cortex, the STN and the PPN (the green arc in the first panel). With regards to a normal situation where nigrostriatal dopaminergic impact is very strong and other dopaminergic pathways including the SNc-PPN one, PD is marked by a disorganization of the network (Panel B) consequent to the loss of dopaminergic transmission. The changes are multiple including the higher strengths of subthalamofugal glutamatergic pathways, the increased activity of the EPN/SNr GABAergic neurons, the decreased PPN connection toward the SNc, and the changes in functional connectivity between the cortex, basal ganglia and PPN (red line). Note that serotonergic and noradrenergic neurons are preserved in most rat models whereas they can be severely damaged (especially noradrenergic neurons) in PD. The administration of L-DOPA enhances dopaminergic transmission in the entire brain because it uses serotonergic pathways, likely increasing DA transmission in the PPN as well. This action counterbalances in part some of the deficits induced by dopaminergic depletion including also the functional connectivity with the cortex and the basal ganglia. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

resting tremor (Qamhawi et al., 2015). The combination of altered neurotransmitter systems could be involved in the therapeutic responses to L-DOPA (Engeln et al., 2015; Jellinger, 1991).

6.1. Mechanism of action of L-DOPA: a PPN involvement?

L-DOPA involved the three monoaminergic systems differently. The increase in DA tissue induced by L-DOPA is widespread in the CNS and concerns several cellular species expressing decarboxylases, the main one being the decarboxylase of aromatic amino acids (AADC) (De Deurwaerdere et al., 2017a). The release of DA is mainly due to serotonergic terminals, a reason why it occurs virtually in all parts of the CNS likely including the PPN (De Deurwaerdere et al., 2017a; Lindgren et al., 2010; Navailles et al., 2010a; Navailles et al., 2010b). This mechanism has also been well studied in neuroimaging studies in humans especially in L-DOPA-induced dyskinesia (Politis et al., 2012; Politis et al., 2014; Smith et al., 2015). The status of the dopaminergic nigro-PPN pathway is altered in PD and MPTP-treated monkeys (Rolland et al., 2009; Ryczko & Dubuc, 2017; Ryczko et al., 2016), reinforcing the impact of the aberrant release of DA by serotonergic terminals in the PPN. While the increase in DA release needs serotonergic terminals almost exclusively in a situation of DA neuron lesion, it occurs at the expense of serotonergic function. The impact of L-DOPA on serotonergic neuronal activity is almost null (Miguelez et al., 2016a; Miguelez et al., 2016b) whereas the biochemical outcomes in terms of release and control of release of 5-HT are highly region-dependent and tends toward a decrease (Miguelez et al., 2016b; Miguelez et al., 2017). It is thus difficult to predict what would be the consequences of acute L-DOPA on 5-HT tone in the PPN; it can be postulated that L-DOPA would reduce the 5-HT tone after chronic administration of moderate to high doses of L-DOPA (Navailles & De Deurwaerdere, 2012; Navailles et al., 2011). Noradrenergic neurons indirectly participate to L-DOPA-stimulated extracellular DA levels by clearing extracellular DA through noradrenergic transporters (NET) (Navailles et al., 2014). This property follows in part the density of the NET in the brain acknowledging that noradrenergic neurons are dramatically reduced in several PD patients (Delaville et al., 2011; Galati & Di Giovanni, 2010). Additionally, L-DOPA is expected to enhance NA release in the brain (Ostock et al., 2018) but the effect is poorly characterized regionally (De Deurwaerdere et al., 2017a), particularly at the level of the dendrites of noradrenergic neurons which are intermingled with PPN neurons (Lavoie & Parent, 1994).

In conclusion, L-DOPA could enhance DA tone by spared 5-HT terminals in the PPN, an effect amplified by the loss of noradrenergic neurons (Fig. 2C). Such an effect could occur with an increase in NA release and a decrease in 5-HT tone, the latter likely conferring a blurry serotonergic transmission in the brain.

Considering the studies above, a role of the PPN in some features of L-DOPA therapy is possible in alleviating akinesia, impairment of sleep, freezing of gait, and possibly dystonia. It is worth noting that the role of striatal DA induced by L-DOPA in alleviating akinesia is presently unclear (Mercuri & Bernardi, 2005). Indeed, motor improvement by L-DOPA can be obtained in experimental situations where almost no striatal DA release can be detected (Carta et al., 2007; De Deurwaerdere et al., 2017a; Navailles et al., 2010b; Porras et al., 2014). It is noteworthy that peripheral L-DOPA in MPTP-treated monkeys can reduce the GABAergic tone in efferent structures of the basal ganglia (at least the thalamus) without any concomitant modification of striatal DA release (Porras et al., 2014).

On one hand, L-DOPA can have effects on its own (Misu et al., 1986; Misu et al., 1995) and several proteins can participate in its mechanism of action (De Deurwaerdere et al., 2017a). On the other hand, the studies evaluating the outcomes of L-DOPA motor effects by destroying serotonergic neurons focused on serotonergic neurons located in dorsal and/or median raphe nuclei (Carta et al., 2007; Navailles et al., 2010b) mostly responsible for the ascending serotonergic innervation. Other serotonergic pathways lying from B1 to B6 nuclei, which are less sensitive to the 5,7-dihydroxytryptamin neurotoxin even after intracerebroventricular injection, are responsible for the septal serotonergic innervation, as well as pontic, medullar or spinal serotonergic innervation (Simic et al., 2017; Steinbusch, 1984). Thus it cannot be excluded that the alleviation of akinesia by L-DOPA also involves

dopaminergic effects in pons, medulla and spinal cord.

6.2. Effect of L-DOPA/DA on PPN activity

Numerous authors tend to conceive PD as a problem of coherence between brain regions involved in motor control and adjustment including the basal ganglia. Using EEG, local LFP or fMRI, it has been reported that DA loss as seen in PD alters the relationships between the PPN and other brain regions including the motor cortex and the basal ganglia (Aravamuthan et al., 2008a; Li et al., 2016; Walters et al., 2007). Notably, it enhanced the power of LFP in PPN and M1 in the low-frequency band and reduced it in the high-frequency band (Geng et al., 2016; Valencia et al., 2014). Chronic L-DOPA treatment could restore the altered power of low field potentials in PPN and M1 in low-frequency band (1-7 Hz) and in the high-frequency band (Geng et al., 2016). The phenomenon has been described in resting and behaving state. The authors used a regimen of L-DOPA (1.5 mg/kg + 1.5 mg/kg of the peripheral decarboxylase inhibitor benserazide three times/day during one week) which is far from restoring DA extracellular levels in the striatum but which already brings up extracellular DA levels over the physiological values in extrastriatal regions (De Deurwaerdere et al., 2017a).

Without any reference to the PPN *stricto sensu*, it has been reported in a recent study addressing the oscillatory responses between the STN, motor and prefrontal cortex in the β- and γ-bands that the alterations produced by the DA lesion were corrected by L-DOPA or apomorphine. The authors conclude that the STN integrates motor and cognitive information that varies with frequency, behavioural state, and the DA tone (Delaville et al., 2015). This is fact compatible with a feedback influence of PPN to the STN, both of them showing some oscillatory synchrony (Li et al., 2016). Moreover, the LFP recorded in the 25–40 Hz in the SNr in unilateral 6-OHDA-lesioned rats were reduced by L-DOPA with a corresponding amelioration of walking. The 5-HT_{1A} receptor agonist 8-OHDPAT counteracted the positive of L-DOPA (Brazhnik et al., 2014).

Irrespective of the presence of a lesion of DA neurons, L-DOPA promotes behavioural activation. L-DOPA (10–20 mg/kg) has been shown to induce EEG activation, arousal and behavioural excitation in rabbits (Ongini et al., 1987). The effects were fully reduced by low dose of the D1 receptor antagonist SCH-23390 whereas only the behavioural effects were reduced by the non-selective D2 receptor antagonist haloperidol. In pups, several research teams have studied the “air” stepping” induced by 100 mg/kg L-DOPA (without peripheral blockade of decarboxylase), a behavioural response thought to mimic spontaneous locomotion. In this model, L-DOPA enhances the air stepping at P15 (or before) and the effect was lost at P20. L-DOPA induced c-Fos expression in output structures of the basal ganglia as well as in the PPN and CuF at P15 whereas this effect was reduced at P25 (Staup & Stehouwer, 2006). For the authors, an inhibitory system which progressively takes place during development counteracts the locomotive effects of L-DOPA seen in early developmental stages. The air stepping effect of L-DOPA has been shown to be dependent on the conversion of L-DOPA into DA and/or NA since it is dose-dependently blocked by the AADC inhibitor NSD1015 (Arnaiz et al., 1996) and can be reported also in decerebrate pups (McCrea et al., 1997). It is also reduced by the dopamine D1 antagonists SCH23390, the D2 antagonist spiperone, the α1 antagonist prazosin or the α2 antagonist idazoxan (McCrea et al., 1997; Sickles et al., 1992; Taylor et al., 1994). At the doses of antagonists used, however, it is difficult to firmly attribute a specific role of the above-mentioned receptors in L-DOPA-induced air stepping. It is also impossible at present to determine the brain location of these effects. It has been recently shown in the lamprey that the application of the D1 antagonist SCH23390 (500 μM) into the MLR reduced the number of locomotor cycles, the frequency of locomotor movements, and the duration of the locomotor bout. The application of DA (5 mM) resulted in the opposite effect (Ryczko et al., 2013). These pharmacological approaches being preliminary, additional data are urgently warranted to further the possibility that DA released in the PPN can play a major role in fine locomotion. Indeed, previous data have reported in cats that the application of DA in the subcoeruleus nucleus (in the vicinity of the PPN) using reverse microdialysis can reduce REM sleep. However, the application of agonists did not mimic DA while D2 receptor agonists rather decreased wakefulness and promote SWS or REM sleep. The effect of DA was blocked by adrenergic antagonists and mimicked by NA and the α2 receptor agonist clonidine (Crochet & Sakai, 1999; Crochet & Sakai, 2003). In MPTP-treated macaques, L-DOPA combined with PPN lesion alleviates sleep disorders (Belaid et al., 2014).

Indirect evidence suggests that some symptoms in PD that refer to gait are associated with changes in 5-HT and derivatives in the CSF of PD patients. Indeed, it has been reported a negative correlation of these parameters with the severity of rigidity, akinesia and Hoehn and Yahr's stages (Tohgi et al., 1993). Postural instability and gait disorder was also associated with decreased CSF 5-HT concentration and increased CSF 5-hydroxytryptophan (metabolic precursor of 5-HT) concentration. The change in the pattern of CSF serotonergic markers seen in the patients being under L-DOPA/AADC inhibitor medication could be consequent to chronic blockade of AADC (Iacono et al., 1997). Paradoxically, the 5-HT_2 receptor antagonist ritanserin has been shown to improve akinesia and gait (Henderson et al., 1992). Thus, a role for 5-HT in some features of PD is likely (Scholtissen et al., 2006a; Scholtissen et al., 2006b) but we cannot clearly associate the mechanisms by which 5-HT acts in the basal ganglia, either with or without interaction with DA systems (De Deurwaerdere & Di Giovanni, 2017), to an action of 5-HT on the MLR.

7. Concluding remarks

The monoamines and the ensemble PPN/LDT in the MLR surely interact in a reciprocal manner to regulate gait, posture and wakefulness. Nonetheless, the anatomical description of possible inputs from monoaminergic systems to the core of the PPN is presently far from clear whereas the influence of the PPN on monoaminergic systems is still poorly known. The availability of new technologies addressing the different, neurochemical populations of the PPN help at deciphering several and subtle influences which were previously difficult to detect. This might be an opportunity to revisit this reciprocal interaction particularly in view of PD therapeutic options including DA replacement therapy and deep brain stimulation.

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