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Review

Cholinergic modulation of midbrain dopaminergic systems

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ABSTRACT

Dopamine neurons in the midbrain respond to behavioral events and environmental stimuli. Their different patterns of activation in turn modulate the activity of forebrain regions and modulate the expression of selective behavioral responses. However, their activity is closely dependent on the cholinergic systems in the brainstem. Ascending cholinergic projections from the pedunculopontine and laterodorsal tegmental nuclei target dopaminergic neurons in the substantia nigra compacta and ventral tegmental area following a topographical gradient. These projections, by means of the activation of acetylcholine receptors, influence the firing of dopamine neurons and therefore their responsiveness, ultimately affecting the release of dopamine in their forebrain targets. Brainstem cholinergic neurons are thus in a position to critically influence the activity of dopaminergic neurons in the midbrain, and thereby have a critical role in the expression of behavior.

Contents

1. Introduction

The pedunculopontine nucleus (PPN) is a neurochemically heterogeneous nucleus situated in the upper brainstem that has been typically associated with the reticular activating system due to its ascending cholinergic projections (Fig. 1). The PPN has a close anatomical relationship with the basal ganglia: every element of the basal ganglia is interconnected either directly or indirectly with the PPN (for a review see Alderson and Winn, 2005; Mena-Segovia et al., 2004a; Pahapill and Lozano, 2000; Garcia-Rill, 1991). This degree of interconnection leads to an interdependence between the two structures that has been

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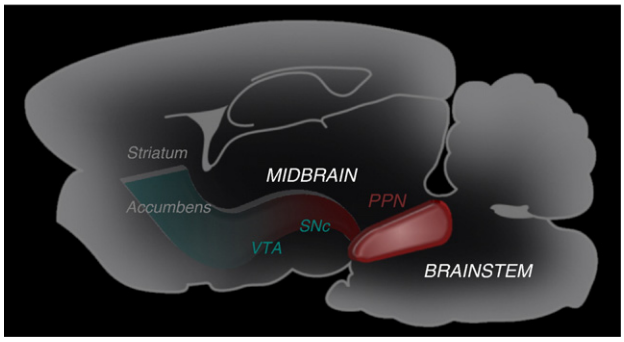

Fig. 1 – Schematic representation of the PPN. Sagittal view of the rat brain showing the location of the PPN in the upper brainstem and the ventral branch of its cholinergic ascending projections (in red). These projections are able to modulate dopaminergic neurons from the midbrain (in green; VTA, ventral tegmental area; SNc, substantia nigra pars compacta) which, in turn, modulate forebrain structures including the striatum and nucleus accumbens.

shown to be involved in some aspects of the pathophysiology of neurodegenerative disorders or their animal models that affect the basal ganglia, such as Parkinson's disease (Breit et al., 2001; Orieux et al., 2000), progressive supranuclear palsy (Kasashima and Oda, 2003; Warren et al., 2005) and Huntington's disease (Mena-Segovia et al., 2004b; Uc et al., 2003). The PPN is able to regulate the activity at three levels of basal ganglia circuitry (Fig. 2). At the first level, which is in close anatomical proximity, PPN neurons have a direct influence on basal ganglia output nuclei, the substantia nigra pars reticulata (SNr) and internal globus pallidus (GPi), and are thus in a position to directly influence the information processed within the basal ganglia before it reaches its targets in, for example, the thalamus. Because of the predominantly excitatory nature of PPN projections, their role may be to facilitate basal ganglia output. A second level of regulation is represented by the interconnections of the PPN with the subthalamic nucleus (STN) that establish a positive feedforward circuit. The projection from PPN to STN converges with inputs from the cortex and external globus pallidus (GPe) and therefore affects the activity of the so-called *hyperdirect* and *indirect* pathways (Bevan and Bolam, 1995). The relationship that PPN maintains with SNr and STN has been shown to be impaired in animal models of Parkinson's disease and, as a consequence of this, PPN has been proposed as a therapeutic target to relieve some of the changes occurring in the basal ganglia. A third level of regulation, which is the subject of the present review, is a function of PPN connections with midbrain dopamine neurons, particularly the substantia nigra pars compacta (SNc) but also the ventral tegmental area (VTA). As is discussed below, activity in this pathway is able to alter dopamine release in the different territories of the striatum (ventral and dorsal), thus affecting other striatal inputs (from cortex and thalamus), and thereby modifying activity in the whole basal ganglia, and ultimately, behavior. This projection has been proposed to be principally cholinergic. A parallel cholinergic input to midbrain dopamine neurons comes from the laterodorsal tegmental nucleus (LDT), a nucleus situated caudal

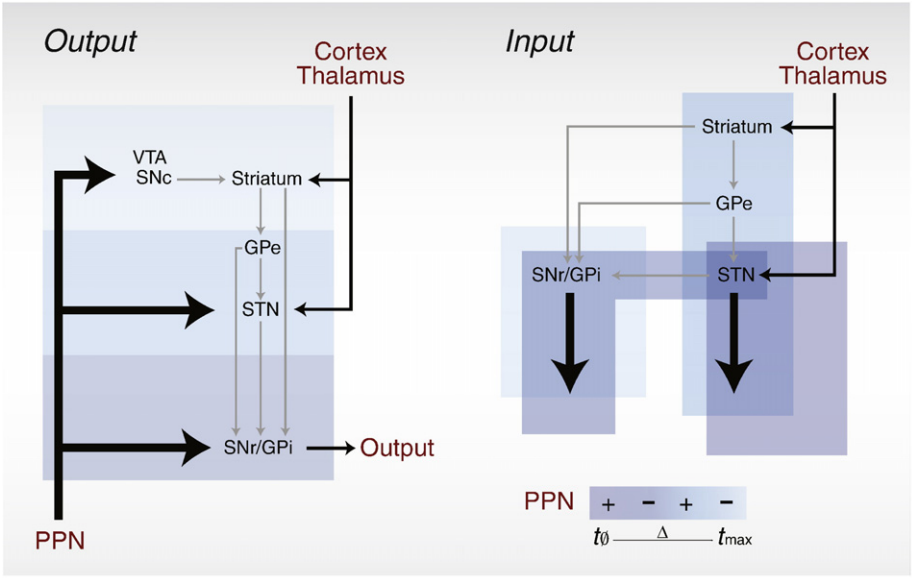

Fig. 2 – Flow of information between the PPN and the basal ganglia. Scheme showing PPN connections with the basal ganglia (thick arrows represent main direct PPN efferent and afferent connections, and gray arrows show internal basal ganglia connectivity): *Left*, PPN neurons project to different levels in the basal ganglia circuits (represented by boxes with different tones of blue; see text). *Right*, the basal ganglia project back to the PPN through projections arising mainly, but not exclusively, in the basal ganglia output nuclei and the subthalamic nucleus (STN). This model of connectivity predicts that activation of the basal ganglia by the cortex will follow different pathways of activation (shown in the boxes) and will eventually reach PPN neurons as a temporal succession of excitatory and inhibitory inputs (represented in the PPN as different tones of blue that correspond to the color tones from the boxes). GPe, external globus pallidus; GPi, internal globus pallidus; SNc, substantia nigra pars compacta; SNr, substantia nigra pars reticulata; VTA, ventral tegmental area.

to the PPN. The LDT has many similarities with the PPN in terms of neurochemical nature (cholinergic, glutamatergic and GABAergic), physiological properties (tonic and phasic wake-related firing) and connectivity (afferents from the lateral hypothalamus, magnocellular area of the basal forebrain, reticular formation and somatosensory brainstem relay nuclei), and indeed the relationship between PPN and LDT could be similar to that between SNc and VTA. Evidence relating to connections and functional interactions will be presented for both structures and will be discussed in the context of the relationship between the mesopontine cholinergic and midbrain dopaminergic systems.

2. Anatomical connections

The analysis of neurons labeled by the juxtacellular method (in which individual neurons were electrophysiologically characterized, labeled with Neurobiotin and then both morphologically and neurochemically characterized) has revealed that individual cholinergic neurons in the PPN project to several targets in the forebrain and lower brainstem. Ventral axon collaterals arising from the proximity of the cell body travel rostrally along the superior cerebellar peduncle and reach several targets in the basal ganglia, including SNr, SNc and STN (Mena-Segovia et al., 2006). Dopaminergic neurons in the SNc receive more dense projections from cholinergic neurons in the PPN than any other neurons in the basal ganglia (Beninato and Spencer, 1987; Beninato and Spencer, 1988; Clarke et al., 1987; Gould et al., 1989; Woolf and Butcher, 1986). The cholinergic innervation arises mainly from rostroventral and medial regions of the PPN (Oakman et al., 1995), and is predominantly ipsilateral, although some degree of contralateral innervation has also been observed (Fig. 3) (Beninato and Spencer, 1987; Clarke et al., 1987; Gould et al., 1989). At the level of the SNc, individual choline acetyltransferase (ChAT)-positive (cholinergic) axons arborize within the SNc but also follow the course of tyrosine hydroxylase (TH)-positive dendrites of dopaminergic neurons. These *climbing* axons give rise to multiple asymmetric synapses contacting dendritic spines, shafts and perikarya. The cholinergic innervation is particularly dense in the distal dopaminergic dendrites enclosed within the boundaries of the SNr, as compared to other parts of the neurons, suggesting a stronger cholinergic effect of these terminals (Bolam et al., 1991). Although LDT cholinergic neurons also project ipsilaterally to SNc dopaminergic neurons, the projection is not as dense as that arising in the PPN (Gould et al., 1989; Oakman et al., 1995; Woolf and Butcher, 1986).

The VTA also has a high density of cholinergic terminals, indicating that it receives a substantial cholinergic input (Henderson and Sherriff, 1991). The VTA receives bilateral innervation from the areas of the highest density of cholinergic neurons in both PPN and LDT (Cornwall et al., 1990; Satoh and Fibiger, 1986), i.e., the dorsocaudal portion and the core of these structures, respectively (Oakman et al., 1995). There is, thus, a topographical gradient of the cholinergic projections from the brainstem, in which SNc is preferentially innervated by rostroventral areas of cholinergic cell groups and VTA is innervated by dorsocaudal areas, suggesting a functional dissociation (specialization) among the cholinergic cell groups (Fig. 3).

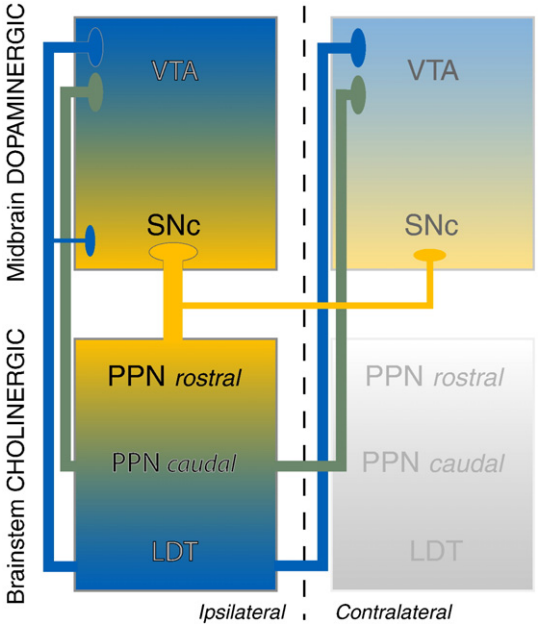

Fig. 3 – Topographical connections between cholinergic neurons and dopaminergic neurons. The projections from the rostral part of the brainstem cholinergic system (PPN rostral) reach the most caudal part of the midbrain dopaminergic system (SNc) and are predominantly ipsilateral (*yellow*), whereas the projections from the medial and caudal parts of the brainstem cholinergic system (PPN caudal and LDT) reach the most rostral part of the midbrain dopaminergic system (VTA) and are bilateral (*blue*).

It is important to note that GABAergic and glutamate neurons are intermingled with cholinergic neurons in the PPN. Non-cholinergic neurons project to the same targets in the basal ganglia as cholinergic neurons, and form part of a local network within the PPN (Mena-Segovia et al., 2006). Furthermore, glutamatergic and GABAergic terminals derived from the PPN have been observed in both the SNc and VTA (Charara et al., 1996; Mena-Segovia et al., 2005). Several studies suggest that the release of glutamate with acetylcholine is important in order to co-activate dopaminergic neurons to produce specific patterns of activity in response to behaviorally relevant stimuli (see next section). What still remains controversial is whether there is co-release of both transmitters from the same terminals: there is evidence for the dual neurochemical nature of PPN neurons (Lavoie and Parent, 1994) but it is also possible that the projections arise from distinct neuronal types, and indeed recent *in situ* hybridization studies show segregated neuronal populations in the PPN and LDT (Marisela Morales, *personal communication*).

3. Responses of dopamine neurons to cholinergic inputs

Dopaminergic neurons show two patterns of activity *in vivo*: they can produce single spikes with a wide range of variation in terms of interspike regularity, or they show burst (phasic) firing. It has been proposed that approximately one third of all

dopaminergic neurons are inactive (hyperpolarized) (Bunney et al., 1991), although a more recent study show that silent neurons in the SNc represent less than 2% of the total population (Dai and Tepper, 1998). The differences between the firing patterns (single spikes *versus* burst firing) seem to depend on the intracellular levels of calcium, through activation of L-type calcium channels (Zhang et al., 2005). Neurons can switch between both conditions after long-term depolarizations induced experimentally by increasing the concentrations of calcium inside the neurons (Grace and Bunney, 1984). Such a change in pattern is usually associated with behaviorally salient stimuli in freely moving animals (for a review see Redgrave and Gurney, 2006).

Acetylcholine receptors have been shown to play a central role in the modulation of the activity of dopaminergic neurons and in determining their burst firing. Neurons in SNc and VTA express somatic and dendritic nicotinic (Clarke and Pert, 1985; Clarke et al., 1985; Sorenson et al., 1998) and muscarinic (Nastuk and Graybiel, 1991) acetylcholine receptors. The presence of several subunits of nicotinic receptors, such as $\alpha 3$, $\alpha 4$, $\alpha 5$, $\alpha 6$, $\alpha 7$, $\beta 1$ and $\beta 2$ (Azam et al., 2002; Jones et al., 2002) has been reported, whereas M5 receptor seems to be most common form of postsynaptic muscarinic receptors. Infusion of nicotine into the SNc produces in dopaminergic neurons *either* a decrease in the input resistance and a transient depolarization of the membrane that results in the generation of action potentials, or an increase in the firing rate if the neuron was already firing (Sorenson et al., 1998). Similar effects have been observed in the VTA (Calabresi et al., 1989) where, after the initial activation, nicotine produces a rapid desensitization (Pidoplichko et al., 1997). In both SNc and VTA, the activation of postsynaptic muscarinic receptors evokes a slower depolarization, but also an increase in the firing rate (Lacey et al., 1990) and burst firing (Zhang et al., 2005). In addition, muscarine is able to decrease the after-hyperpolarizations following action potentials, which would facilitate firing at higher frequencies and possibly bursting (Scroggs et al., 2001). Several mechanisms have been proposed to explain how the activation by acetylcholine might facilitate burst firing, including an increase in the levels of intracellular calcium mediated by NMDA receptors (Kitai et al., 1999), activation of L-type calcium channels (Zhang et al., 2005), and the mobilization of calcium from internal stores. All of these support the idea that the switch from single spike firing to burst firing following the activation of acetylcholine receptors is a calcium-dependent mechanism.

Electrical stimulation of the PPN typically produces a robust excitatory response in the SNc (Scarnati et al., 1984) mediated by acetylcholine and glutamate (Futami et al., 1995; Scarnati et al., 1986). Furthermore, this stimulation *in vivo* is able to produce one-to-one time-locked bursts, whose latency is independent of the current intensity, suggesting that the effect is monosynaptic (Lokwan et al., 1999). In the VTA, afferents from the PPN also produce an increase in the number of neurons firing in a bursting pattern, although this effect is produced only in neurons that were already firing — PPN inputs do not appear to be able to recruit inactive neurons or increase the firing rate of active neurons (Floresco et al., 2003). In contrast, chemical stimulation of the LDT by infusion of a glutamate agonist or a muscarinic antagonist increases the number of active neurons in the VTA. Interestingly, the inactivation of the LDT by the administration of GABA agonists produces a pronounced decrease in the burst firing of dopamine neurons in the VTA that is not reversed by PPN stimulation (Lodge and Grace, 2006). During LDT inactivation, VTA neurons fire tonically in a very regular pattern, resembling the pacemaker firing pattern observed *in vitro* (Grace and Onn, 1989).

In summary, cholinergic neurons of the brainstem regulate the firing rate of midbrain dopaminergic neurons and determine their burst firing. Supported by the anatomical data, these studies also support the notion of a functional segregation of cholinergic projections over the nigrostriatal and mesolimbic systems, in which PPN is able to modulate the activity of SNc and VTA, and the LDT predominantly influences the latter.

4. Cholinergic modulation of dopamine neurons: functional impact in the striatum and nucleus accumbens

Activation of cholinergic neurons in the brainstem produces an increase in dopamine release in the striatum and the nucleus accumbens through the activation of acetylcholine receptors in the SNc and VTA, respectively (Blaha et al., 1996; Blaha and Winn, 1993; Chapman et al., 1997; Dewey et al., 1993; Hernandez-Lopez et al., 1992; Kudernatsch and Sutor, 1994; Marchi et al., 1992). An initial fast onset increase in dopamine release (as measured by chronoamperometry) seems to be primarily dependent on nicotinic and ionotropic glutamate receptors (Forster and Blaha, 2003), and is followed by a late and sustained increase in dopamine levels that is dependent on M5 muscarinic receptors (Miller and Blaha, 2005). A transient decrease in striatal dopamine release occurs after the fast nicotinic activation but before the late muscarinic-induced release, and has been shown to be mediated by M2 muscarinic receptors in the region of the cholinergic somata, suggesting a feedback inhibitory mechanism in cholinergic neurons (Forster and Blaha, 2003). The late muscarinic-dependent component of dopamine release seems to be independent of nicotinic and ionotropic glutamate receptors, and is significantly higher in magnitude and duration. Conversely, the blockade of muscarinic receptors in SNc and VTA is associated with a decrease in the dopamine release in the striatum and nucleus accumbens, which suggests that a basal cholinergic tone is required to maintain basal dopamine levels (Blaha and Winn, 1993; Dewey et al., 1993; Forster and Blaha, 2003; Miller and Blaha, 2005).

Single spike firing of dopaminergic neurons is able to produce dopamine release in the striatum, although the burst firing pattern is probably more a determinant of dopamine release. With the concomitant use of a blocker of the dopamine transporter, a significant increase in dopamine levels was observed in the nucleus accumbens following the infusion of a GABA antagonist in the PPN, a condition that has previously been shown to increase bursting activity (Floresco et al., 2003). Thus, the differences in release associated with the different firing patterns reflect two dynamic states in the levels of dopamine in the striatum and nucleus accumbens: a tonic state, with low but steady levels of dopamine, and a phasic state, associated with behavioral events and responses

to environmental stimuli. Such characteristics, in turn, reflect the attributes of the cholinergic inputs, which might provide a functional *duality*: to ensure the basal level of responsiveness of dopamine neurons (stimulus-unspecific and anatomically diffuse) but also to drive the response required in precise circumstances (stimulus-specific and anatomically localized).

5. Behavioral correlates

It is clear that acetylcholine has a role in regulating the activity of midbrain dopamine neurons, and as such has a part to play in shaping behavior. This was first recognized in the 1970s, when Stanislaw Wolfarth presciently suggested that "*the substantia nigra may be one of the structures which is a central point of cholinergic – dopaminergic equilibrium*" (Wolfarth, 1976). In order to understand the nature of this equilibrium it is important to have a context in which it can be established. This context is set by consideration of the functions of the striatum, where dopamine is released. Striatal functions are commonly discussed in terms of associative conditioning, with the functions of different territories given different, but inter-related properties. For example, core and shell of the nucleus accumbens have roles in instrumental responding and response rate respectively, while the dorsomedial striatum is important for action–outcome association learning and the dorsolateral striatum habit (or stimulus–response) learning (see Everitt and Robbins, 2005 for review). This behavioral organization can be seen as representing a ventral to dorsal shift across the striatum, from highly goal directed processes in which the purposes of actions are of particular importance, towards processes that are less goal directed and to do with the elicitation of habitual responses to particular stimuli, with less regard to the goal of the action. This is consistent with the spiral relationship that exists between striatum and midbrain dopamine neurons (Haber et al., 2000).

The behavioral functions of midbrain dopamine neurons are also characterized in terms of learning. These neurons respond to many activating stimuli, but the degree to which they are predictable appears to be a key determinant of firing. It has been argued that midbrain dopamine neurons produce a reinforcement error prediction signal (Schultz, 1998) and that phasic activation of the firing of midbrain dopamine neurons is maximal in conditions of high uncertainty (when the probability that a stimulus signals reward is 0.5) and lowest in conditions of certainty (when the probability that a stimulus signals reward is either 0 or 1; Fiorillo et al., 2003). Can the behavioral functions of cholinergic inputs to midbrain dopamine neurons be characterized in the same way? Three lines of evidence suggest that they can.

(i) Early data indicate that microinjection of cholinergic drugs into the substantia nigra potentiates any activity, providing there is a low current rate and a pre-existing tendency to respond (Winn et al., 1983). This potentiation of activity without special regard to goals, is consistent with the hypothesis that the dorsal striatum has a role to play in stimulus–response, habitual, control. (ii) An even closer parallel exists in the relationship between the VTA and ventral striatal structures that have goal-directed functions. For example, both rats (Ikemoto and Wise, 2002) and mice (David et al., 2006) will self-administer cholinergic drugs directly into the VTA. Both nicotine and the muscarinic and nicotinic agonist, carbachol, are self-administered, though perhaps surprisingly, carbachol is the more potent than nicotine. Intra-VTA administration of nicotine tends not to occur on first presentation but can develop over time, whereas carbachol is self-administered immediately an animal determines which lever will deliver it. It is conceivable that this is related to the triphasic activation of dopamine release (Forster and Blaha, 2003), with the fast nicotinic action and slower, more sustained muscarinic activation having different psychological properties. (iii) Studies of PPN suggest that it has important functions related to learning. Electrophysiological studies in cats (Dormont et al., 1998) and rats (Pan and Hyland, 2005) support this. The activity of PPN neurons is not related to movement *per se* but instead appears be related to the occurrence of events that predict reward. Pan and Hyland (2005) note that these neurons might have a particular role in coding the timing of sensory events, information that would be needed by dopamine neurons in delivering a fast phasic reinforcement prediction error signal. A role for the PPN in learning is also suggested by the effects of excitotoxic lesions, which produce behavioral changes that are not characterized by motor impairment. Rather, the changes observed indicate "higher order" functions for the PPN (see Winn, 2006 for review). On the basis of a series of studies, Alderson and Winn (2005) argued that a core deficit produced by excitotoxic lesions of PPN is impaired action–outcome association learning. The extent to which these effects derive from disruption of cholinergic transmission in the midbrain is uncertain, but it is of interest that the effects described are at least consistent with there being loss of cholinergic control of dopamine neurons. The development of new tools with which to manipulate cholinergic functions in the mesopontine tegmentum and midbrain will be of benefit in resolving this (Clark et al., 2007; Maskos et al., 2005).

6. Conclusions

Two interrelated systems arise from the cholinergic brainstem neurons but maintain a degree of segregation at the level of the dopamine systems in the midbrain and the different striatal territories they innervate. The cholinergic projections arising from the LDT target mainly neurons in the VTA, influence their burst firing and the consequent release of dopamine in the nucleus accumbens, and probably influence goal directed behaviors. In contrast, the cholinergic projections arising from the PPN have a wider influence over the midbrain dopamine systems, as PPN neurons innervate both SNc and VTA neurons. They seem to be less critical in controlling the burst firing and population activity of dopamine neurons. Instead, PPN neurons could be more implicated in maintaining the muscarinic-dependent tonic release of dopamine, but would also be able to provide phasic signals for dopamine neurons to time sensory events (and therefore its role in associative learning). This "phasic function" is likely to also underlie its role as a part of the reticular activating system and the contribution of acetylcholine to the coherence in thalamocortical neurons in the integration of sensory stimuli.

Nevertheless, the roles of these two cholinergic systems, LDT and PPN, should not be seen as entirely segregated, but rather complementary. Indeed, they could be conceived as one single structure with different areas of specialization that follow a topographical gradient. These areas of specialization might then represent their association with afferent systems: in addition to the inputs that both cholinergic structures share (see Introduction), the LDT receives preferential innervation from the prefrontal cortex and lateral habenula, whereas the PPN receives strong inputs from the basal ganglia (as discussed above), bed nucleus of the stria terminalis and the central nucleus of the amygdala (Semba and Fibiger, 1992), thus supporting the idea of functional segregation. Moreover, anatomical evidence of reciprocal connections between LDT and PPN, as well as local interconnections in the PPN, form the basis of a functional microcircuit capable of performing *early* processing of environmental information, before sending the information out to the dopamine systems. Further experiments detailing the nature of the interactions between LDT and PPN are necessary to precisely define the contributions of cholinergic neurons to the activity of midbrain dopamine neurons, and to better characterize the dual nature of the cholinergic drive (modulatory role versus stimulus specific activation).

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