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Descending dopaminergic control of brainstem locomotor circuits

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The locomotor role of meso-diencephalic dopaminergic (DA) neurons is traditionally associated with their ascending pathways to the basal ganglia, which project to the Mesencephalic Locomotor Region (MLR), a brainstem region controlling locomotion. However, descending DA projections to the MLR were recently reported in lamprey, where they promote locomotion through the activation of D_1 receptors in the MLR. In rodents, the DA innervation of the MLR is conserved and originates from the *substantia nigra pars compacta* (A9) and medial *zona incerta* (A13). Intriguingly, the DA innervation of the MLR degenerates in a monkey model of Parkinson's disease. Here, we review the current knowledge on these newly uncovered descending DA pathways to brainstem circuits and discuss their possible roles in locomotor control.

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Introduction

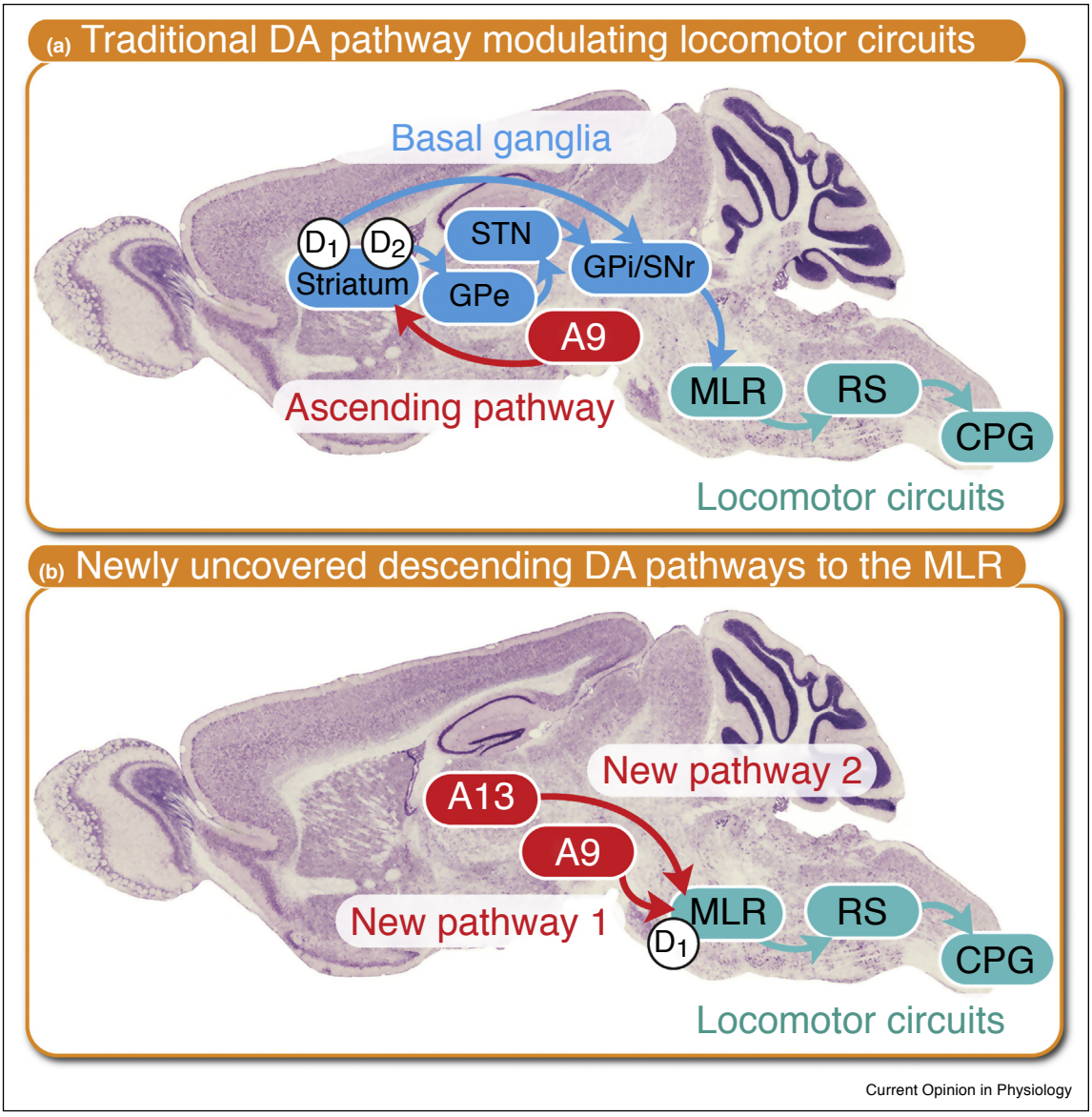
In vertebrates, the dopaminergic (DA) system plays a key role in modulation of locomotor activity. Molecules increasing the availability of dopamine at the synapse, such as amphetamine (a psychostimulant) or levodopa (a dopamine precursor), are well known to increase locomotor activity. Conversely, the loss of DA cells in Parkinson's disease results in motor dysfunction, including severe locomotor deficits (gait freezing, falls). Traditionally, meso-diencephalic DA cells are considered to modulate locomotion through their ascending projections to the basal ganglia, which project to the Mesencephalic Locomotor Region (MLR). This brainstem region sends the locomotor command to the reticulospinal neurons, which relay it to the spinal locomotor circuits. However, recent studies uncovered that DA cells also send direct descending projections to the MLR from basal vertebrates to mammals [1••,2,3••,4,5••]. In lamprey, these descending DA projections [1••,2,3••,4] promote locomotion by potentiating glutamatergic inputs to the MLR through the activation of D_1 receptors [1••,4]. In mammals, the MLR receives DA innervation not only from the *substantia nigra pars compacta* (A9) (new pathway 1) [3••] but also from the medial *zona incerta* (A13) (new pathway 2) [5••] (Figure 1). Thus, in addition to the ascending pathway to the basal ganglia that in turn project to the MLR, meso-diencephalic DA cells have two descending pathways through which they possibly exert a control on the MLR. Another diencephalic group of DA cells located in the hypothalamus (A11) sends descending projections directly to the spinal cord, and this could contribute to regulate some aspects of the locomotor pattern by releasing dopamine on neurons of the central pattern generator. We will not extensively review the literature concerning the A11 pathway (for review, see Ref. [6]). Here, we will focus on the two descending DA pathways innervating the MLR.

Traditional DA pathways to locomotor circuits

Soon after the discovery of dopamine in the brain, pioneering work in patients with Parkinson's disease revealed that the loss of the ascending projections from meso-diencephalic DA neurons to the basal ganglia play a key role in locomotor control ([7], for review see Ref. [8]). Within the basal ganglia, the effects of dopamine involve the direct and indirect pathways, which are conserved from basal vertebrates to mammals ([9–13, 14••, for review see Ref. [15]). Through the 'direct pathway', dopamine increases the excitability of D_1-expressing cells in the striatum, and this results in relieving the inhibition sent by the basal ganglia output station to the MLR, resulting in locomotion initiation (Figure 1a). Through the 'indirect pathway', dopamine this time decreases the excitability of the D_2-expressing neurons in the striatum, and this also results in decreasing the inhibition sent by the basal ganglia to the MLR [14••] (Figure 1a). Thus, loss of the ascending DA projections to the striatum results in locomotor dysfunction most likely through overinhibition of the MLR (see Ref. [10]).

The spinal cord is also a target for DA modulation of locomotor activity. Pioneering work in spinalized cats showed that systemic injection of levodopa evokes reciprocal discharges in hindlimb flexor and extensor nerves [16], promotes stepping movements of intact limbs [17], or induces locomotor-like rhythmic discharges in

Figure 1



The descending dopaminergic (DA) pathways to the Mesencephalic Locomotor Region (MLR). **(a)** The MLR comprises the the pedunculopontine nucleus (PPN) and the cuneiform nucleus (CnF). The CnF and PPN send descending projections to reticulospinal (RS) nuclei that in turn project to the spinal central pattern generator (CPG) for locomotion. The ascending DA pathway from A9 to the striatum (the entry station of the basal ganglia) is illustrated. Within the basal ganglia, D_1-expressing striatal neurons of the '*direct pathway*' and D_2-expressing striatal neurons of the '*indirect pathway*' and their targets are illustrated. **(b)** The descending DA pathways from the *substantia nigra pars compacta* (A9) to the MLR (new pathway 1) and from the medial *zona incerta* (A13) to the MLR (new pathway 2) are highlighted with red arrows. In lamprey, the descending DA pathway provides excitation to the MLR through the activation of D_1 receptors [1••,4]. The photograph illustrating a Nissl staining of the mouse brain was kindly provided by GENSAT. GPe; *globus pallidus pars externa*, GPi, *globus pallidus pars interna*; STN, subthalamic nucleus.

hindlimb nerves [18]. More recently, work in isolated spinal cords has strengthened the idea that the central pattern generator for locomotion is modulated by dopamine. Overall, D_1 receptor activation enhances rhythm stability and D_2 receptor activation decreases it (e.g. in *Xenopus laevis* [19], lamprey [20] or neonatal mice [21,22]), but such effects may vary depending on the excitability level of the central pattern generator [22]. An important diencephalic source of spinal DA innervation is A11 in mice [23] and primate [24] (for review see Ref. [[27••]]). In zebrafish, some diencephalic DA neurons projecting to the spinal cord were proposed to be homologous to the mammalian A11 DA nucleus [25]. During spontaneous bouts of fictive locomotion in zebrafish, these DA neurons

switch from tonic to bursting activity. Ablation of these DA neurons results in less locomotor bouts, without modifying the parameters of motor output, suggesting that these neurons regulate the excitability of the spinal locomotor circuit [26]. A recent study revealed that optogenetic activation of DA neurons in A11 increases locomotor activity in mice, and this effect could involve a direct modulation of spinal locomotor circuits [27••] (for review, see Ref. [[27••]]).

Two new DA pathways to brainstem locomotor circuits

Recent studies uncovered that the MLR receives direct descending projections from meso-diencephalic DA neurons in lamprey [1••,[3••],4], salamander [3••], rat [3••], mouse [5••], and likely monkey [28••] and human [3••] (Figure 1b). Such descending projections were first characterized in lamprey. The MLR was shown to receive direct descending DA projections from a region proposed to be homologous to A9, because of its ascending projections to the striatum [1••,[3••],4]. Stimulation of this DA region evoked dopamine release in the MLR [1••], which was closely associated in time with the initiation of spiking activity in reticulospinal neurons that carry the locomotor command to the spinal cord [1••]. The descending DA projections to the MLR play an important role in locomotor control in lamprey. In a semi-intact preparation where the basal ganglia were removed, stimulation of the DA region evoked swimming [1••,4]. Increasing the stimulation intensity in the DA region progressively activated MLR cell activity and gradually increased swimming speed [4]. Interestingly, the descending DA pathway is paralleled by a glutamatergic one, and many DA neurons co-store glutamate [4]. The glutamatergic component plays a key role in providing excitation to the MLR, and the DA component amplifies it [4]. Blockade of D_1 receptors in the MLR decreased the frequency of swimming movements and the duration of the locomotor bout evoked by stimulation of the DA region [1••,4].

In salamanders, the descending projections from meso-diencephalic DA neurons are conserved [3••]. As in lampreys, the DA release recorded in the MLR was closely associated with the activation of reticulospinal neurons [3••]. As in other vertebrates, reticulospinal neurons play a crucial role in carrying the MLR locomotor command [29] controlling stepping and swimming movements in this animal [30]. This suggests that DA release in the MLR likely plays a role in the increase in locomotor activity evoked by systematic administration of amphetamine in salamanders [31].

Before describing the DA innervation of the MLR in mammals, it is useful to underline the recent studies that elegantly established that the MLR is a heterogeneous structure (for recent review see Ref. [32]). Briefly, the mammalian MLR comprises the cuneiform nucleus (CnF) and the pedunculopontine nucleus (PPN). The CnF receives inputs from regions processing threatening stimuli, such as the amygdala, hypothalamus, and periaqueductal gray, whereas the PPN receives inputs from brain regions involved in action selection and goal-directed behavior, such as the basal ganglia and motor cortex (for review see Ref. [33]). The CnF comprises glutamatergic and GABAergic cells, whereas the PPN comprises glutamatergic, cholinergic, and GABAergic cells [14••,34,35]. CnF and PPN glutamatergic cells play a key role in locomotion initiation, because they project to reticulospinal neurons that carry the locomotor drive to the spinal cord [36], as in basal vertebrates [37,29]. In mice, optogenetic activation of CnF glutamatergic cells controls both the slow gaits (walk, trot) and the fastest gaits (gallop, bound) used during escape behaviors [34,35]. Optogenetic activation of PPN glutamatergic cells rather controls solely the slow gaits (walk and trot) for the purpose of exploratory behavior [34,35]. Optogenetic activation of GABAergic cells in the CnF or PPN stops locomotion, likely through local inhibition of the glutamatergic cells [34,35,14••]. The role of PPN cholinergic cells is not resolved. In mice, their optogenetic activation can increase [35,14••] or decrease locomotor speed [34]. In lamprey, the highest swimming speeds cannot be reached without the cholinergic component of the MLR, which activates muscarinoceptive cells in the brainstem that feed additional drive onto reticulospinal neurons [38]. In monkeys and humans, loss of PPN cholinergic cells is associated with locomotor and postural deficits such as those seen in Parkinson's disease [39]. This is consistent with neurophysiological studies suggesting an additional role for the PPN in postural control [40].

In mammals, both the PPN and CnF are innervated by DA fibers. In rats, fibers positive for tyrosine hydroxylase (TH) or for the dopamine active transporter (DAT) were found in proximity with PPN cholinergic cells [3••], where the best locomotion-inducing stimulation sites are located [41]. The origin of this pathway was determined using virogenetic tracing in animals expressing the Cre-recombinase in TH-positive neurons (TH-Cre rats). An adeno-associated virus injected in the PPN retrogradely labelled several TH-positive cells in A9 [3••]. This was confirmed using conventional dextran amine injection in the PPN-coupled with immunofluorescence against TH [3••]. Several A9 cells were found to send both descending projections to the PPN and ascending projections to the striatum [3••]. In addition, electrical stimulation of A9 evoked DA release in the PPN *in vivo* in rats. Such release was potentiated by systemic injection of amphetamine [3••], suggesting that the hyperlocomotor effects of DA drugs such as psychostimulants or levodopa could involve DA release in the MLR. In monkey [28••] and human [3••], TH-positive and DAT-positive terminals were found

around the cholinergic cells of the PPN as well. Altogether these data indicate that the descending projections from meso-diencephalic DA neurons are a conserved feature of the DA system in vertebrates.

Interestingly, a recent study in mice showed that the MLR receives another descending DA pathway from the medial *zona incerta* (A13), located in the ventral thalamus [5••]. Using retrograde virogenetic tracing in TH-Cre mice, the authors found that 30% of A13 DA neurons project to the CnF, and 21% project to the PPN [5••]. Anterograde virogenetic labelling of descending fibers from A13 DA neurons combined with analysis of synaptic puncta revealed that the CnF receives a denser DA innervation than the PPN [5••]. Contrary to A9, A13 was not found to send ascending projection to the striatum [5••]. Another remarkable difference with A9 is that A13 DA neurons do not express DAT [5••]. This suggests that dopamine released by A13 may have longer effect kinetics on their targets. This also suggests that the DAT-positive fibers reported in the rat PPN [3••], do not originate from A13. They likely do not originate from A11 DA neurons as well, which also lack DAT expression in mouse [23], monkey [24] and human [42]. Future studies should determine whether activation of DA neurons in A13 can evoke locomotion. Interestingly, previous reports have shown that increase in locomotor activity can be evoked by pharmacological activation or disinhibition of the *zona incerta* [43–45].

Relevance to dopamine function and pathological states

DA neurons appear to modulate in parallel the basal ganglia and brainstem motor circuits from basal vertebrates to mammals. This raises the key question of the respective contributions of the ascending and descending DA pathways in locomotor control. The ascending projections from A9 DA neurons to the basal ganglia are well known to be involved in action selection and goal-directed behavior [9,46,10,13,15]. Interestingly, recent studies highlighted the strong link between A9 DA cell activity and locomotor activity. In mice, increased activity in A9 DA neurons precedes locomotion initiation, whereas decreased activity in A9 is associated with locomotion termination [47–49]. Optogenetic activation of A9 DA neurons initiates locomotion [47,48], whereas their inactivation disrupts locomotion initiation [49]. Future studies should determine whether descending projections from A9 DA neurons are involved is these locomotor effects. We propose that the descending DA inputs from A9 increase the excitability of PPN cells to make them 'ready-to-go' for exploratory locomotion when the inhibition from the basal ganglia is released. In contrast with A9, A13 DA cells do not send ascending projections to the striatum [5••], and rather projects to brain regions processing threatening stimuli or promoting avoidance behavior like the periaqueductal grey or the superior colliculus [50,51], and the CnF, involved in escape locomotion [33,34]. Interestingly, the connectivity of the PPN and CnF, respectively, mirrors those of A9 and A13, suggesting the A9 and A13 could regulate distinct aspects of locomotor behavior [33,34,52].

The DA innervation of the MLR could play a role in the physiopathology of Parkinson's disease. Severe locomotor deficits appear when DA cells degenerate [39,53]. Classically, these deficits are attributed to the loss of the ascending DA projections to the basal ganglia [7,10,14••]. However, the descending DA innervation to the MLR also degenerates in a monkey model of Parkinson's disease [28••]. This could cause a loss of amplification of the locomotor commands, resulting in locomotor deficits [1••,3••,4, for review see Ref. 54]. Beyond locomotor control, recent studies indicate that brainstem regions involved in visual and auditory processing are also targeted by descending projections from meso-diencephalic DA neurons. In lampreys, descending DA projections influence the detection of a target in the visual field through the innervation of the optic tectum, a brainstem region controlling eye movements [55]. Interestingly, this region is homologous to the mammalian superior colliculus [55], which is also modulated by dopamine in rodents [50,51]. In addition, descending projections of A11 release dopamine in auditory brainstem regions including the inferior colliculus in rodents [56,57]. Thus, loss of the descending DA inputs to the brainstem could also play a role in abnormal auditory processing and abnormal eye movements in Parkinson's disease [56,57], in addition to locomotor deficits [54].

Conclusions

Altogether, these studies bring a new light on the role of DA neurons in locomotor control. It now appears that the meso-diencephalic DA neurons can influence different components of the locomotor circuitry by sending ascending projections to the basal ganglia, descending projections to brainstem locomotor circuits and descending projections to the spinal cord. As recently underlined by experts of the neurobiology of Parkinson's disease [58], future studies should determine the role of the descending DA pathways to the MLR in physiological and pathological states in mammals.

Conflict of interest statement

Nothing declared.

Author contributions

M.F. A.F. A.F. and D.R. wrote the paper.

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