A basis for the pathological oscillations in basal ganglia: the crucial role of dopamine

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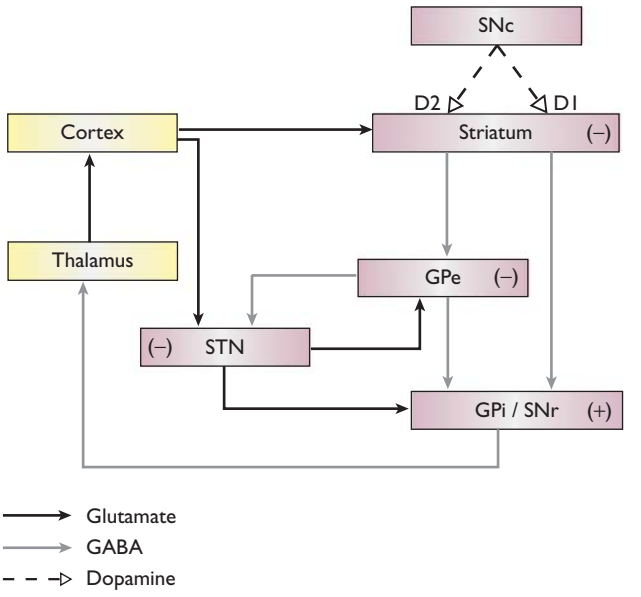
Introduction

Parkinson's disease is a progressive neurodegenerative movement disorder characterized by reduction and slowness of movement (akinesia and bradykinesia), muscle rigidity, and tremor. The core pathology of the disease is the degeneration of midbrain dopaminergic neurons in the substantia nigra pars compacta that project to the striatum and other basal ganglia nuclei. The striatum is the main input structure of the basal ganglia and receives excitatory projections from many cortical areas and thalamic nuclei. The output neurons of the striatum, named as medium spiny neurons, are γ-aminobutyric acidergic (GABAergic) and project to both the globus pallidus internus and externus, and to substantia nigra pars reticulata, which are also GABAergic. The other nucleus within the basal ganglia is the subthalamic nucleus that receives direct cortical inputs and an input from the globus pallidus externus and its glutamatergic neurons project to the globus pallidus internus and substantia nigra pars reticulata (see Fig. 1).

Until recently it was thought that the loss of dopaminergic inputs to the striatum led to hyperactivity of the globus pallidus internus and substantia nigra pars reticulata, and this caused hypokinetic motor symptoms. This model, frequently termed as the 'rate' model, provided a very plausible explanation for the bradykinesia and akinesia that develops in Parkinson's disease, as the proposed hyperactivity of the GABAergic output nuclei, globus pallidus internus, and substantia nigra pars reticulata would lead to hypoactivity in the thalamic relay to motor cortex, thus, leading to a decreased cortical excitability and slowness and reduction of movements. Initial experimental evidence provided support for this model and was the basis for introduction of pallidotomies and deep brain stimulation in the subthalamic nucleus and globus pallidus internus for treating Parkinson's disease. However, recent findings have cast doubt on the validity of this model and prompted a re-examination of the mechanisms underlying the symptoms of Parkinson's disease [1]. In particular, electrophysiological recordings in corticobasal ganglia circuits in animal models and patients with Parkinson's disease showed that chronic dopamine depletion is associated with alterations in firing patterns and oscillatory activity and it is now widely believed that these changes play a more important role in mediating the pathophysiology than changes in firing rates.

Many of these advances were facilitated by the opportunity afforded by the therapeutic procedure of implantation of deep brain stimulation electrodes in the subthalamic nucleus and globus pallidus internus, which permitted the recordings of neuronal acitivity and local field potentials in patients with Parkinson's disease. In addition, the use of animal models with Parkinson's disease, in particular, monkeys treated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and rats treated with 6-hydroxydopamine,

Fig. 1



Simplified diagram of basal ganglia connections. Excitatory and inhibitory connections are distinguished by black and gray lines respectively. The overall direct effect of dopamine on synaptic transmission in each nucleus is indicated by the (+) and (−) signs. D1 and D2, dopamine receptor subtypes; GABA, γ-aminobutyric acid; GPe, globus pallidus externus; GPi, globus pallidus internus; SNc, substantia nigra pars compacta; SNr, substantia nigra pars reticulata; STN, subthalamic nucleus.

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chemicals leading to substantia nigra pars compacta cell death has permitted investigation of the effects of dopamine depletion on the function of basal ganglia.

There is growing evidence that increased synchrony between neurons and increased oscillatory firing within the basal ganglia play a key role in the pathophysiology of Parkinson's disease. The origin of these pathological activities, however, is still under extensive investigation and is reviewed below.

Pathological oscillations in Parkinson's disease

The loss of dopaminergic input to the striatum leads to excessive synchronized oscillatory firing within the basal ganglia-cortical loops and was first reported in monkeys treated with MPTP. Later on, the presence of exaggerated oscillatory activity of single neurons and neuronal populations as reflected in the oscillatory local field potential activity, especially within the subthalamic nucleus and globus pallidus, was seen in recordings from patients with Parkinson's disease, who were withdrawn from their antiparkinsonian medications [2]. The oscillatory discharges occurred mainly in two frequency bands: the tremor frequency (which is mainly seen in tremulous patients) and the β frequency (between 11 and 35 Hz). The presence of β oscillations was also reported in the 6-hydroxydopamine rat model of Parkinson's disease [3].

The link between synchronized oscillations and dopamine depletion is most clearly shown by the fact that treatment with dopaminergic agents rapidly reduces oscillatory and synchronized firing [2], but the mechanisms by which dopamine exerts these effects are still unclear. As the basal ganglia–thalamo–cortical loop is to some extent a closed circuit, oscillations are likely to emerge and spread out within this loop. Indeed, there is evidence for increased functional connectivity and coherence between cortex, subthalamic nucleus, and pallidum in the dopamine-depleted state [3–6]. However, little is known about the cellular and network mechanisms underlying the generation and propagation of these oscillations through the basal ganglia, or why this synchronized oscillatory activity results in bradykinesia.

Basis of neuronal oscillations in the dopamine-depleted basal ganglia

Dopamine depletion leads to increased excitability of striatal neurons

Medium spiny neurons normally display a very polarized resting potential (down state) that is interrupted by robust depolarizing events (up state). Down states are determined by inwardly rectifying potassium currents that clamp the membrane potential at a hyperpolarized level, whereas up states are initiated and maintained by concurrent excitatory inputs. Action potential discharges occur only during the up states, when the excitatory inputs are strong enough to overcome the various inhibitory forces generated by the rectifying currents, and by feedforward and feedback inhibitions from local interneurons and axon collaterals, respectively [7]. Thus, the plateau depolarizations in medium spiny neurons allow 'reading' of cortical information by the basal ganglia.

Dopamine plays a key role in modulating the up and down states of medium spiny neurons. After dopamine depletion, striatal medium spiny neurons exhibit shorter and less hyperpolarized down states, and fire more frequently in conjunction with cortical inputs [8,9]. After systemic administration of D1 receptor agonists, most medium spiny neurons become silent. In addition to its postsynaptic modulation, dopamine directly inhibits glutamate release from corticostriatal terminals by stimulating D2 receptors located on a subpopulation of cortical afferents [10]. Thus, presynaptic D2 receptors, together with postsynaptic D1 receptors, provide a mechanism for modulating cortical signals. Dopamine loss therefore facilitates the passage and spreading of cortical rhythms throughout the basal ganglia network by disrupting striatal 'filtering' of cortical inputs.

Apart from depolarizing medium spiny neurons, dopamine loss has been shown to facilitate electrotonic coupling between neighboring striatal neurons [11]. This effect was hypothesized to result from upregulation of gap junctions, which might further facilitate interactions and synchronization among the neurons.

Altered striatal-globus pallidus transmission

Findings in the striatum and globus pallidus in rodents (which is equivalent to the primate globus pallidus externus) support the view that after dopamine loss, an increase in striatal output contributes to the emergence of oscillations in the globus pallidus externus [12]. Moreover, in addition to its effect on the striatum, dopamine acts directly on extra-striatal basal ganglia nuclei. In the globus pallidus, dopamine acts to increase the neuronal activity by attenuating GABAergic inhibition. This is mediated by activation of presynaptic D2 receptors on striatopallidal terminals, which reduces GABA release [13,14], and by activation of postsynaptic D4 receptors that inhibit GABA receptor-mediated currents [15]. The loss of GABAergic inhibition in the globus pallidus externus can potentially amplify synchronized oscillations within the subthalamic nucleus-globus pallidus externus network (see below).

In the globus pallidus internus (entopeduncular nucleus in rodents), in contrast, dopamine acts on presynaptic D1-like receptors and enhances GABA release from terminals of the striato-globus pallidus internus projections, therefore, reducing neuronal activity in the globus pallidus internus (and the same is true for substantia nigra pars reticulata) [16,17]. Activation of D1-like receptors increases oscillatory and bursting firing in the globus pallidus internus in both normal monkeys and monkeys treated with MPTP, whereas blockade of these receptors has the opposite effect [17,18].

This effect is paradoxical as increased bursting and oscillatory activities resemble the pathological state, suggesting that reduced dopamine action in globus pallidus internus does not contribute to the oscillatory firing there after dopamine depletion in animals and patients with Parkinson's disease. Instead, network interactions may be more important in determining these abnormalities, which would be consistent with the finding that the transmission of information between the primary motor cortex and the globus pallidus is greatly enhanced after treatment with MPTP [6].

Spontaneous activity in subthalamic nucleus neurons: from tonic firing to bursts

The subthalamic nucleus is densely populated by glutamatergic projection neurons, which are capable of firing independently of synaptic input because of their pacemaker voltage-gated sodium channels. These neurons are most likely to display tonic firing, and only very few spontaneously fire in bursts [19]. The vast majority of the neurons, however, can switch from a relatively regular firing pattern to an irregular/bursting pattern under various conditions [20–22].

In animal models with Parkinson's disease and patients with Parkinson's disease, a significantly higher proportion of subthalamic nucleus neurons display burst-like firing patterns, as opposed to regular discharge characteristic of the nonparkinsonian state. D1-like agonists increase the spontaneous and stimulation-evoked firing rates of tonic subthalamic nucleus neurons, and D2-like agonists influence bursting neurons by reducing their burst duration and turning bursting into a tonic firing pattern [19,23]. Thus, concurrent activation of D1 and D2 receptors promotes tonic firing of subthalamic nucleus neurons. Moreover, by acting on postsynaptic D2-like receptors, dopamine increases the variability of autonomous firing of subthalamic nucleus neurons, and acts to decorrelate subthalamic nucleus activity [24]. Thus, in the dopamine-depleted state there is enhancement of the intrinsic membrane properties that enable synchronized burst firing.

In addition to its effect on spontaneous firing patterns, dopamine binding to presynaptic D2 receptors reduces the release probability of glutamate and GABA [25,26] and thus suppresses both glutamatergic excitatory postsynaptic potentials (EPSPs) and GABAergic inhibitory postsynaptic potentials (IPSPs) in subthalamic nucleus [25,27]. Dopamine loss therefore results in enhanced synaptic input to the nucleus, and this contributes even further to the emergence of synchronized oscillations (discussed below).

Subthalamic nucleus-globus pallidus externus network: enhanced feedback inhibition and rebound bursting

The globus pallidus externus is reciprocally connected with the subthalamic nucleus (see Fig. 1), creating a network that can potentially generate and maintain low-frequency (approximately 5 Hz) rhythmic activity in the absence of cortical and striatal input [28]. This low-frequency pacemaker activity has the potential to facilitate the faster oscillations that are observed *in vivo* in the parkinsonian state. Extrastriatal dopaminergic modulation is thought to sustain the normal interaction between subthalamic nucleus and globus pallidus externus and its loss may therefore contribute to pathological oscillatory activity.

The autonomous activity in subthalamic nucleus leads to increased numbers of inactivated sodium channels, which can be transiently deinactivated by the hyperpolarization induced by the pallidal input. Thus, if the inhibitory input is strong enough to completely reset the autonomous activity, it can promote synchronization because it results in deinactivation of all of the voltage-gated sodium channels that underlie the autonomous activity [20]. In contrast, weak individual IPSPs promote only partial resetting of subthalamic nucleus neurons, which results in variable delays between spikes and desynchronization among the neurons. Strong multiple IPSPs do not only reset subthalamic nucleus firing, but also occasionally promote rebound bursts by bringing the membrane potential to a more hyperpolarized state, which primes low-threshold calcium channels and hyperpolarization-activated cationic currents that are not active during spontaneous activity [20,22].

These various properties suggest that feedback inhibition from the globus pallidus externus has the potential to synchronize the activity of subthalamic nucleus neurons. As dopamine acts locally to reduce inhibitory synaptic input to the subthalamic nucleus [25,29], its absence may enhance the impact of synchronous GABAergic inputs. In addition, dopamine acts in the globus pallidus both presynaptically through D2/3-like receptors and postsynaptically through D4-like receptors to reduce excitatory subthalamopallidal input [30]. Thus, its absence may facilitate the excitatory feedback from subthalamic nucleus to globus pallidus externus, and thus strengthen the spatiotemporal rhythmic and synchronous oscillatory activity in the subthalamic nucleus-globus pallidus externus network.

After the loss of dopamine, pallidal oscillatory firing is influenced more by inhibitory input from the striatum than by excitatory input from the subthalamic nucleus [12]. This is in contrast to the normal situation in which the firing of pallidal neurons is entrained by excitatory subthalamic nucleus input [31]. Thus, the level of dopaminergic stimulation is an important factor in determining the relative influence of the striatum versus the subthalamic nucleus on the globus pallidus externus.

Enhancement of cortico-subthalamic integration

As subthalamic nucleus neurons are the only glutamatergic neurons of the basal ganglia, they can function as a direct excitatory relay through which cortical information reaches the output nuclei of the basal ganglia.

As mentioned earlier, hyperpolarizing events in subthalamic nucleus neurons can potentially increase their firing by decreasing the number of inactivated voltage-gated sodium channels. Indeed, the coupling between postsynaptic EPSPs and the number of action potentials is dramatically increased when IPSPs precede EPSPs [32]. Thus, enhanced GABAergic inhibition from globus pallidus externus can prime subthalamic nucleus neurons to respond more efficiently to excitatory cortical input by increasing the availability of voltage-gated sodium channels. In Parkinson's disease, the loss of dopamine in the subthalamic nucleus amplifies feedback inhibition from the globus pallidus externus. This increased feedback inhibition, together with the enhanced release probability in subthalamic nucleus synapses, enhances the effectiveness of cortical inputs to generate action potentials by reducing threshold, latency, and variability [33]. Furthermore, the synchrony between cortical neurons is enhanced after treatment with MPTP [34], thus providing a more powerful oscillatory input to the subthalamic nucleus.

In dopamine-depleted animals, the interaction between the subthalamic nucleus and cortical areas is enhanced, and low-frequency oscillations become apparent in the globus pallidus and are correlated with cortical oscillatory activity [3,4]. The oscillatory activity is abolished by ipsilateral cortical ablation, suggesting that abnormal oscillatory activity in the subthalamic nucleus-globus pallidus externus network in the dopamine-depleted state is generated by inappropriate enhanced processing of β oscillatory inputs originating in the cortex.

Evidence from studies in patients with Parkinson's disease

Similar to the observations in animal models, the oscillatory activity seen in patients with Parkinson's disease is suppressed by dopamine replacement therapies, in tandem with clinical improvement [2]. Recent evidence has emerged of an interesting correlation between the amount of β activity in the subthalamic nucleus of patients with Parkinson's disease and the improvement in motor symptoms after intake of dopaminergic medication [35–37]. This raises the possibility that the amount of oscillatory activity reflects the sensitivity of the network, or at least the subthalamic nucleus, to dopamine. Approximately a quarter of the neurons in the subthalamic nucleus show oscillatory firing at either β or tremor frequency [35,38], and some can alter their oscillatory firing from one frequency to another over time [38]. It is therefore tempting to hypothesize that the frequency of oscillations is being determined by an external source of input to the subthalamic nucleus. In fact, the oscillatory firing of subthalamic nucleus neurons is almost always time-locked to the simultaneously recorded local field potentials, which are believed to be generated by the temporal summation of postsynaptic potentials and hence to reflect synchronized inputs [35,39].

The cortex is a likely source of rhythmic oscillatory inputs to the basal ganglia, especially through the subthalamic nucleus. The oscillatory activity (in both the neuronal firing and local field potentials) is maximal in the dorsal part of the subthalamic nucleus [35], which is known to receive input from the primary motor cortex [39]. Further evidence for the cortical origin of oscillations comes from electroencephalographic recordings in patients with Parkinson's disease, who show abnormal β-band synchronization of cortical networks that is coherent with the oscillatory activities in subthalamic nucleus and globus pallidus internus [5]. Furthermore, transcranial magnetic stimulation of the primary motor and supplementary motor cortical areas significantly suppresses β activity in the subthalamic nucleus [40], also suggesting that the cerebral cortex drives and/or enhances basal ganglia β oscillations in Parkinson's disease.

Table 1 Summary of the mechanisms involved in the generation and propagation of oscillatory activity within the basal ganglia after dopamine loss

	Presynaptic and postsynaptic actions of dopamine in the basal ganglia			
Site of action	Striatum	STN	GPe	GPi
Postsynaptic	Promotes down state of MSNs and filtering of cortical rhythms	Enhances uncorrelated tonic firing	Reduces GABA-mediated and subthalamopallidal currents	
Presynaptic	Inhibits corticostriatal glutamate release	Reduces release of glutamate and GABA	Reduces GABA release at striatal synapses and glutamate release at STN synapses	Enhances GABA release at striatal synapses
Effects of dopamine loss on basal ganglia neurons				
	Enhances cortical inputs to the striatum	Enhances intrinsic bursting activity	Enhances responses to striatal inputs	Enables efficient transfer of STN rhythmic inputs
	Disrupts striatal filtering and enhances response to cortical oscillations	Enhances GPe-induced hyperpolarization and rebound STN bursting	Promotes synchronized bursting activity driven by STN	
	Facilitates electrotonic coupling	Enhances direct cortical driving		
Overall effect	Promotes synchronized oscillatory bursting activity in the basal ganglia network			

GABA, γ-aminobutyric acid; GPe, globus pallidus externus; GPi, globus pallidus internus; MSNs, medium spiny neurons; STN, subthalamic nucleus.

Our recordings in subthalamic nucleus and globus pallidus internus in patients with Parkinson's disease and dystonia show that there can be considerable variability in the coupling between local field potentials, which primarily reflect synaptic inputs, and neuronal firing and suggest that at least a part of this variability is related to extrastriatal dopamine levels. This situation is also predicted on the basis of the experimental findings regarding dopamine's presynaptic and postsynaptic actions as discussed above. Thus, in patients with Parkinson's disease one generally observes many neurons in subthalamic nucleus and globus pallidus internus with strong oscillatory bursting coherent with the β frequency oscillatory local field potential activity when off dopaminergic medication but much less when they are on medication. In contrast, in patients with dystonia the incidence of globus pallidus internus cells with oscillatory activity coherent with the local field potential is significantly lower than in patients with Parkinson's disease (unpublished data). Table 1 summarizes the proposed mechanisms involved in the generation of oscillatory activity in the basal ganglia network after dopamine depletion.

In summary, the data from patients with Parkinson's disease add to the growing evidence emerging from animal models and in-vitro studies that dopaminergic loss in Parkinson's disease may increase the sensitivity of the basal ganglia–thalamo–cortical network to rhythmic oscillatory inputs, perhaps of cortical origin, leading to pathological oscillatory synchronization within and between these structures which interferes with the processing of movement-related signals and results in motor deficits.

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