REVIEW ARTICLE

Synaptic and cellular plasticity in Parkinson's disease

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Parkinson's disease (PD) is a progressive neurodegenerative disease, which causes a tremendous socioeconomic burden. PD patients are suffering from debilitating motor and nonmotor symptoms. Cardinal motor symptoms of PD, including akinesia, bradykinesia, resting tremor, and rigidity, are caused by the degeneration of dopaminergic neurons in the substantia nigra pars compacta. In addition, decreased amounts of dopamine (DA) level in the basal ganglia induces numerous adaptive changes at the cellular and synaptic levels in the basal ganglia circuits. These cellular and synaptic adaptations are believed to underlie the emergence and propagation of correlated, rhythmic pattern of activity throughout the interconnected cortico-basal ganglia-thalamocortical network. The widespread pathological pattern of brain activity is closely linked to the devastating motor symptoms of PD. Accumulating evidence suggests that both dopaminergic degeneration and the associated abnormal cellular and circuit activity in the basal ganglia drive the motor symptoms of PD. In this short review I summarize the recent advances in our understanding of synaptic and cellular alterations in two basal ganglia nuclei (i.e. the striatum and the subthalamic nucleus) following a complete loss of DA, and in our conceptual understanding of the cellular and circuit bases for the pathological pattern of brain activity in parkinsonian state.

Keywords: Parkinson's disease; dopamine; basal ganglia; striatum; subthalamic nucleus; synaptic plasticity

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INTRODUCTION

The basal ganglia are a group of interconnected subcortical brain regions that transform cerebral cortical activity into common behaviors [1]. The basal ganglia are important for a variety of brain functions and behaviors, such as action selection, habit formation, cognition, and motor control [1–3]. In mammals, the basal ganglia comprise the striatum, the external and internal segments of the globus pallidus (GPe and GPi), the subthalamic nucleus (STN), and the substantia nigra pars compacta and reticulata (SNc and SNr). The striatum and the STN are two input stations of the basal ganglia, and they receive topographically organized excitatory inputs from the cerebral cortex and thalamus; the SNr and the GPi are the major outputs of the basal ganglia, transmitting processed information to downstream motor regions (Fig. 1a), including the thalamic nuclei, which are responsible for the planning and execution of skilled movements, the pedunculopontine, which is important for the regulation of locomotor activity, and the superior colliculus, which contributes to the control of eye movements [1, 2, 4].

The striatum is the largest component and the main input structure of the basal ganglia, and it receives major excitatory inputs from layer V glutamatergic pyramidal neurons of the cerebral cortex. GABAergic spiny projection neurons (SPNs) are the principal neurons in the striatum and represent 90% of all striatal cells. Two biochemically and anatomically distinct types of SPNs give rise to the so-called "direct" and "indirect" pathways of the basal ganglia, which process afferent information directly or indirectly to basal ganglia outputs, respectively.

Direct pathway SPNs (dSPNs) express D1-like receptors (D1Rs) and project directly to neurons in the SNr/GPi, while indirect pathway SPNs (iSPNs) express D2-like receptors (D2Rs) and project to the GPe, which in turn is connected to the STN through GABAergic synapses, forming the classical indirect basal ganglia pathway [2, 5] (Fig. 1a). The STN is another major input station of the basal ganglia, and STN neurons release the neurotransmitter glutamate. STN neurons receive monosynaptic inputs from the cerebral cortex (Fig. 1a), forming the "hyperdirect" pathway [6, 7].
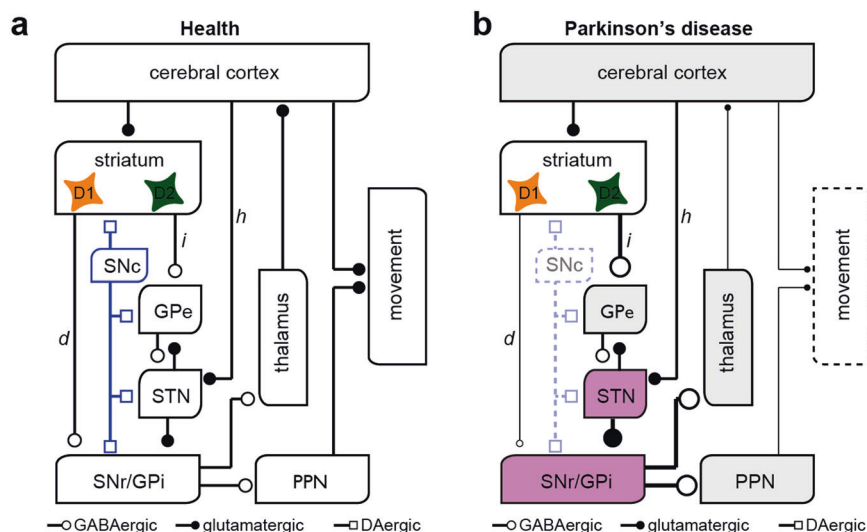
Based on the classical model of the basal ganglia, excitatory cortical inputs are dynamically processed through the direct, indirect, and hyperdirect pathways to the basal ganglia output stations, the SNr and the GPi (Fig. 1a). SNr/GPi neurons exhibit a high level of spontaneous firing at rest, which tonically inhibits downstream motor areas, such as the motor thalamus and brain stem [4, 8]. The activation of dSPNs increases GABA release and thus decreases the activity of neurons in the SNr/GPi, which in turn reduces tonic inhibitory outputs to downstream motor regions and thus promotes movement. On the other hand, the activation of iSPNs or STN neurons produces a net excitatory effect on SNr/GPi neurons through either disinhibition or direct excitation mechanisms; this effect in turn elevates GABAergic outputs to downstream motor areas and thus inhibits movement [2, 4]. Recent advances in neurotechnology for neural circuit manipulation have made it possible to directly test the relationship between the anatomical connections of the basal ganglia and behavioral effects. For example, the stimulation of dSPNs and iSPNs using

Fig. 1 The classical model of the basal ganglia under healthy condition and in PD. **a** In the healthy brain, the main excitatory inputs to the basal ganglia arise from the cerebral cortex and enter the basal ganglia through both the striatum and the STN. Cortical excitatory inputs are processed through the direct (*d*), indirect (*i*), and hyperdirect (*h*) pathways to influence the neuronal activity of the basal ganglia output nuclei, the SNr/GPi, which, in turn, regulate the activity of downstream motor control areas in the brain stem and thalamic nuclei. Dopaminergic projections (blue) from the SNc dynamically modulate cellular activity in the basal ganglia through D1 or D2 receptors. **b** In the parkinsonian state, the degeneration of SNc DA neurons and the loss of dopaminergic projections result in the hyperactivity of indirect pathway SPNs, the hypoactivity of neurons in the GPe (gray), and the disinhibition of the STN and GPi/SNr (red), ultimately leading to enhanced inhibition of motor regions in the brain stem and thalamus (gray) and reduced movements

optogenetic or chemogenetic tools increases and decreases, respectively, the motor activity of animals [9–11], which is largely in line with the classical model of the basal ganglia (Fig. 1a).

Over the last 30 years, the classical model has greatly shaped our understanding of the physiology of the basal ganglia, the pathophysiology of basal ganglia-related neurological diseases, and the development of surgical approaches for the treatment of Parkinson's disease (PD). However, the classical model has been challenged by recent advances in our understanding of the anatomy, physiology, and behavioral relevance of the basal ganglia. For example, studies using in vivo electrophysiology recording and imaging techniques have suggested that temporally coordinated activation of dSPNs and iSPNs is required to successfully initiate, execute, and complete specific movements [12–14]. This is in contrast to the classical model of basal ganglia, i.e., a simple "Go/No-Go" relationship between the direct and indirect pathways. Moreover, synaptic connections in the basal ganglia are usually bidirectional rather than unidirectional, as suggested by the classical model [15]. For example, reciprocal synaptic projections between the GPe and the STN (Fig. 1a) have been established and characterized by anatomical studies for decades and implicated in the propagation of pathological activity throughout the cortico-basal ganglia-thalamocortical network [16, 17]. In addition, the heterogeneity of cell types and synaptic connections is increasingly recognized as a common feature of the basal ganglia circuits [15, 18–21]. The best example is the heterogeneity of GPe neurons as well as their complicated local and long-range connections [15, 18, 22–24]. The functional implications and behavioral relevance of these cell-type- or brain-region-specific projections are not fully understood. Furthermore, SNc DA neurons corelease GABA and glutamate at their axon terminals [25–27], which greatly affects how DA neurotransmission modulates the synaptic and cellular properties of postsynaptic targets and basal ganglia-related behavior.

THE BASAL GANGLIA MODEL OF PD PATHOPHYSIOLOGY

SNc dopaminergic neurons send prominent dopaminergic projections to striatal SPNs and other basal ganglia nuclei (Fig. 1a). In the healthy brain, the release of DA upon the firing of these DA neurons dynamically modulates the synaptic and intrinsic properties of postsynaptic targets depending on their expression of distinct DA receptor subtypes [28]. Striatal dSPNs and iSPNs express D1- and D2-like receptors, respectively, and they respond differently upon DA neurotransmission because of the distinct intracellular signaling cascades involved. In brief, DA release increases the activity of striatal dSPNs by stimulating $G_{s/olf}$-coupled D1 receptors and decreases the activity of iSPNs by stimulating G_i-coupled D2 receptors. Thus, striatal DA release favors the activity of the direct pathway over that of the indirect pathway. The net effect of DA release in the striatum is a decrease in basal ganglia output, which disinhibits the thalamic nuclei and brain stem, leading to the initiation and execution of normal movements.

In the parkinsonian state, however, the loss of DA in the striatum decreases the activity of dSPNs and their excitability in response to cortical excitation, which ultimately disinhibits GABAergic projection neurons in the SNr/GPi. In parallel, the loss of DA in the striatum increases iSPN excitability and enhances the sensitivity of iSPNs to cortical excitation through the elimination of D2 receptor-mediated inhibition. Increased striatal inhibition of GPe neurons disinhibits STN activity, leading to enhanced STN-mediated excitation of neurons in the SNr/GPi (Fig. 1b). Therefore, the loss of DA disrupts the balance in activity between the striatal direct and indirect pathways and enhances inhibitory basal ganglia outputs to the motor thalamus and brain stem, ultimately leading to a reduction in motor outputs (Fig. 1b). The imbalance in activity between the direct and indirect pathways of the basal ganglia following the loss of DA is the dominant theory regarding the pathophysiology of motor deficits in PD, such as paucity and slowness of movements. This theory was proposed based on evidence and observations from animal models of complete DA depletion or from postmortem examination of brain tissues from end-stage PD patients [2]. Considering the progressive nature of

DA degeneration in PD and the different sensitivities of distinct subtypes of DA receptors to DA, exploration of the temporal evolution of the imbalance in activity between the direct and indirect pathways of the basal ganglia as PD progresses is critically needed. Such knowledge would help to establish the relationship between the level of DA depletion, the relative activity of the striatal direct and indirect pathways, and the severity of motor dysfunction.

Recent advances in experimental tools, particularly techniques for in vivo cell labeling and identification and in vivo Ca^{2+} imaging, have made it possible to measure the neuronal activity of different cell subtypes in specific brain regions under both healthy and disease conditions. For example, the hyperactivity of striatal iSPNs compared to dSPNs has been demonstrated using in vivo electrophysiology recording techniques that monitor the spontaneous activity of these two SPN subtypes in both rat and mouse models of PD [29, 30]. Of particular interest, Escande et al. [31] recently demonstrated that dSPNs, but not iSPNs, show a reduced number of spikes upon stimulation of the cerebral cortex after partial nigrostriatal DA depletion. Thus, the imbalance in activity between the direct and indirect pathways can be caused by either increased iSPNs excitability or decreased dSPNs responsiveness to excitatory inputs. Furthermore, the findings of Escande et al. also indicate that the balance in activity between the striatal direct and indirect pathways may be disrupted in the early stages of PD, i.e., prior to the onset of motor symptoms. What is the precise nature of the brain dysfunction that determines the onset of motor deficits in PD? Future studies focusing on adaptive changes outside of the striatum are needed to address this fundamental question.

As mentioned earlier, precise coordination between the activity of dSPNs and iSPNs is required for the successful initiation and execution of specific movements in normal animals, and DA transmission is a crucial factor in determining the temporal profiles of striatal SPNs activation [32]. Consistently, cell-type-specific optogenetic manipulation of SPNs activity in vivo either slows, prolongs, or stops the initiation and execution of an action sequence [13]. It seems plausible that the loss of DA neuromodulation in the parkinsonian state disrupts the temporal pattern of coordinated activity between the striatal direct and indirect pathways during movement. Indeed, by monitoring the population activity of SPNs in parkinsonian and control mice, Parker et al. [33] demonstrated that DA depletion in locomoting mice disrupts both the firing frequency and the temporospatial profiles of SPNs activity. Interestingly, the population activity of iSPNs in the parkinsonian state becomes spatially dispersed and shows reduced temporal coupling at the start and end of movements [33]. This study highlights the importance of coordinated activity of neural ensembles in the striatum for normal motor control and suggests that the disruption of the coordination and specificity of SPNs perhaps contributes to motor impairments in PD. This study is of particular importance to the field because it conceptually advances our understanding of PD pathophysiology at the cellular and circuit levels.

CELLULAR AND CIRCUIT ADAPTATIONS IN THE STRIATUM IN PD
The classical basal ganglia model of PD pathophysiology was proposed based on the acute effects of DA depletion on cellular and synaptic properties in the striatum. However, the neural network is not static. Neurons in the brain are capable of stabilizing cellular and network functions through a series of synaptic and cellular adaptations (i.e., homeostatic plasticity mechanisms) in response to external and internal disturbances [34]. Indeed, numerous molecular, cellular, and synaptic adaptations in the basal ganglia have been reported following the loss of SNc dopaminergic neurons. Some of these alterations have been

proposed to be compensatory in nature, stabilizing cellular and circuit functions associated with lower amounts of DA in the basal ganglia. Others, however, are perhaps pathological, contributing to the manifestation of motor impairments in PD. The following sections summarize recent findings of morphological and functional alterations in two major input nuclei, the striatum and the STN, at the cellular and circuit levels following the loss of DA and discuss the potential roles of these adaptive alterations in the pathophysiology of the motor symptoms of PD.

DA DEPLETION REWIRES LOCAL STRIATAL CIRCUITS
Early studies of postmortem tissues from PD patients demonstrated apparent alterations in the morphologies of SPNs, such as a significant reduction in the length of the dendritic tree and a loss of spine density [35, 36]. These findings from postmortem analysis of end-stage PD were subsequently confirmed in neurotoxin-based animal models of PD using either Golgi impregnation of fixed brains [37] or two-photon live-cell imaging [38, 39]. Of particular interest, both dSPNs and iSPNs of 6-OHDA-lesioned mice show reduced dendritic length and decreased dendritic spine density, but only changes in iSPNs can be reversed by prolonged L-DOPA treatment [39]. The distinct effects of L-DOPA on morphological alterations in dSPNs and iSPNs suggest that the shrinkage of the dendritic tree and loss of spines of iSPNs are direct consequences of DA depletion, whereas structural alterations in dSPNs are due to the secondary effects of DA depletion, such as network effects.

In addition to morphological changes, the loss of DA triggers a homeostatic increase in intrinsic dSPNs excitability and a decrease in intrinsic iSPNs excitability [39, 40]. Moreover, Gittis et al. [41] demonstrated that DA depletion increases inhibitory inputs to iSPNs from parvalbumin-expressing interneurons. Therefore, DA depletion rewires the local circuit of the striatum by decreases the intrinsic excitability of iSPNs, decreasing corticostriatal synaptic density, and increasing GABAergic inhibition. Considering the hyperactivity of iSPNs in PD, these cellular and synaptic alterations may be homeostatic mechanisms that stabilize striatal function and delay the onset of motor deficits in PD. Concurrently, homeostatic plasticity also occurs in dSPNs to compensate for their hypoactivity following the loss of DA through an increase in intrinsic excitability [39]. Interestingly, L-DOPA treatment can fully restore the altered intrinsic excitability of iSPNs but only mildly affects the intrinsic excitability of dSPNs [39]. These observations suggest the engagement of different mechanisms (cell-autonomous versus network mechanisms) in regulating the intrinsic plasticity of SPNs in the parkinsonian state [42].

LONG-TERM SYNAPTIC PLASTICITY OF STRIATAL EXCITATORY SYNAPSES IN PD
Striatal SPNs are capable of exhibiting long-term potentiation (LTP) and long-term depression (LTD) at corticostriatal synapses, although different molecular mechanisms are involved in long-term synaptic alterations in dSPNs and iSPNs [43, 44]. Shen et al. [43, 45] demonstrated that LTP induction in dSPNs is mediated by the activation of NMDA receptors and D1 receptors, whereas LTD induction depends on the activation of muscarinic M4 receptors and mGluR5 receptors. In iSPNs, LTP induction depends on the activation of A2A receptors and NMDA receptors, whereas LTD induction is gated by postsynaptic D2 receptors and mGluR5 receptors [43]. Thus, striatal dSPNs and iSPNs are capable of either the potentiation or depression of synaptic inputs in the normal state, and this bidirectional regulation of synaptic strength is precisely regulated by neuromodulators. However, bidirectional synaptic plasticity at corticostriatal synapses is disrupted in a cell-type-specific manner in the parkinsonian state, i.e., LTP and LTD at corticostriatal synapses are selectively impaired in dSPNs and

iSPNs, respectively [43, 44]. In parkinsonian animals, LTP is abolished in dSPNs because of the absence of D1R activation, and LTD is abolished because of a lack of D2R activation. Thus, iSPNs only exhibit LTP, whereas dSPNs only show LTD in DA-depleted animals [43]. While bidirectional synaptic plasticity at corticostriatal synapses under healthy conditions is required for motor learning and normal motor control, unidirectional synaptic plasticity at corticostriatal synapses following the loss of DA plays a critical role in the disruption of the balance between dSPNs and iSPNs activity [43, 44] and thus is an important cellular and circuit mechanism associated with PD pathophysiology.

In addition, Parker et al. [46] reported abnormal strengthening of thalamostriatal inputs to iSPNs but not to dSPNs following the loss of DA. The chemogenetic or optogenetic inhibition of thalamic inputs to iSPNs ameliorates motor dysfunction in a 6-OHDA-lesioned model of PD, indicating that such strengthening is maladaptive in nature. Although the molecular and cellular mechanisms underlying thalamocortical remodeling remain unknown, this study further emphasizes the importance of investigating PD pathophysiology in a cell-type- and input-defined manner. Most studies in the literature have used 6-OHDA to induce complete DA depletion to mimic end-stage PD; thus, we have little information about the cell-type-specific synaptic plasticity alterations in the presence of different striatal DA levels, which represent distinct stages of PD [47].

CELLULAR AND CIRCUIT ADAPTATIONS IN THE STN IN PD
STN neuronal firing under healthy conditions and in PD
STN neurons receive monosynaptic cortical excitatory inputs through the hyperdirect pathway, and they receive major inhibitory inputs from the GPe, which forms part of the indirect pathway [2, 6, 7] (Fig. 1a). Thus, the STN is at the intersection of the hyperdirect and indirect pathways and plays a critical role in movement control by integrating and transmitting movement-related information to basal ganglia outputs. STN neurons spontaneously fire action potentials in vivo [48–50], and the rate and pattern of STN discharges vary under different physiological states. A battery of ionic mechanisms that give rise to the autonomous activity of STN neurons has been determined using brain slice physiological approaches [51, 52]. Moreover, both excitatory and inhibitory inputs play important roles in the control of STN neuronal activity under both healthy and disease conditions [52]. During slow-wave sleep and under urethane anesthesia, synchronized excitatory glutamatergic inputs from the cerebral cortex drive STN neuron firing in rhythmic bursts of action potentials (approximately 1 Hz) [53, 54]. Moreover, perisomatic GABAergic inputs from the GPe have been proposed to effectively reset the oscillatory cycle of ionic mechanisms underlying the rhythmic firing of STN neurons and thus promote burst firing of action potentials through GABA$_A$ receptor-mediated inhibitory postsynaptic potentials [17, 55].

Topographically, the dorsolateral part of the STN is responsible for processing motor-related information [56], and this is also the region that show prominent pathological activity in PD [57–59]. In idiopathic and experimental models of PD, STN neurons are hyperactive and exhibit synchronized rhythmic activity that is highly correlated with cortical and GPe activity [16, 60]. Indeed, pathological oscillations (particularly the β band between 13 and 30 Hz) are prominent throughout the cortico-basal ganglia-thalamocortical network [57, 61], which is closely linked to motor symptoms in PD, such as akinesia and rigidity. For example, the abnormal coherent and rhythmic activity within the cortico-basal ganglia-thalamocortical network can be concurrently suppressed by symptomatic PD treatment, including dopaminergic replacement therapy and deep brain stimulation [62–64]. Of particular interest, the abnormal rate and pattern of STN activity emerge weeks after the loss of DA in neurotoxin-based animal models of

PD [60, 65], indicating the involvement of cellular and synaptic plasticity in its emergence, development, and stabilization.

Synaptic and cellular plasticity of STN neurons in PD
As discussed above, DA depletion induces numerous synaptic and cellular plasticity processes in the striatum, which favors the hyperactivity of iSPNs and leads to enhanced striatal inhibition of prototypical GPe neurons and disinhibition of STN neurons (Fig. 1b). Based on the classical model, STN hyperactivity in the parkinsonian state is a network phenomenon rather than a cell-autonomous increase in intrinsic excitability. Indeed, STN neurons in brain slices derived from 6-OHDA-lesioned mouse models of PD show decreased, irregular, spontaneous firing [66–69]. McIver et al. [68] recently reported that in PD, abnormal spontaneous firing of STN neurons is associated with activated ATP-sensitive K$^+$ channel function due to reduced ATP production by impaired mitochondria. Excessive NMDA receptor activation in the parkinsonian state impairs the mitochondrial function of STN neurons, although the source of glutamatergic excitation that tonically stimulates NMDARs has not yet been defined. Considering the presence of STN hyperactivity in patients and animal models of PD, a decrease in the intrinsic excitability of STN neurons can act as a homeostatic mechanism for stabilizing cellular and circuit function.

What are the potential network mechanisms that underlie the pathological rate and pattern of STN activity in vivo? STN neurons are autonomously active and are driven by a group of voltage-gated ion channels [51, 52]. The rhythmic membrane cycle underlying the autonomous firing of STN neurons can be effectively shifted by cortical excitation and GPe inhibition [51, 52]. Moreover, DA depletion alters the responsiveness of both the glutamatergic and GABAergic receptors of STN neurons [70], indicating adaptive changes at the cellular level. Fan et al. [71]. and Chu et al. [72]. provided molecular, anatomical, and functional evidence that the inhibitory GPe-STN synaptic connection is abnormally strengthened following the loss of DA through an increase in the number of release sites per GPe-STN axon terminal. This abnormal strengthening of the GPe-STN synaptic connection is mediated by the excessive activation of NMDA receptors in the STN and can be reversed by the genetic knockdown of NMDA receptors in STN neurons in vivo [72]. The abnormal strengthening of GP-STN synapses is pathological in nature because its prevention by genetic manipulation ameliorates motor impairments in parkinsonian mice [72].

In parallel with abnormal strengthening of inhibitory GP-STN synapses, a dramatic reduction in the number of cortico-STN synaptic terminals and synaptic connection strength have been reported in both rodents and primate models of PD [69, 73, 74]. These synaptic adaptations significantly rewire the local circuit in the STN and dramatically shift the excitation-to-inhibition balance of STN neurons. Furthermore, in the parkinsonian state, the activity of STN neurons is off-phase to GPe activity and in-phase to cortical activity [16, 60]. Thus, it is predicted that GPe-STN inhibitory inputs are less effective in suppressing cortical excitation through shunting but more effective in promoting the cortical mediation of STN activity through deactivation of postsynaptic voltage-gated Na$^+$ and Ca^{2+} channels, which are the ionic mechanisms underlying the generation of the rhythmic activity of STN neurons [55]. Therefore, enhanced connections between the cerebral cortex and the STN (the hyperdirect pathway) in PD are largely driven by aberrant temporal interactions between pallidal inhibition and cortical excitation in the STN rather than strengthening of cortico-STN synaptic connections per se. In other words, the relative synaptic strength and timing of cortico-STN excitation and GPe-STN inhibition following a loss of DA are the major circuit mechanisms that drive the synchronized and coherent activity of STN neurons in vivo. Moreover, the effectiveness of dopamine-targeting drugs or deep brain stimulation of the STN is believed to be mediated by the disruption or

suppression of aberrant oscillatory activity within the cortico-basal ganglia-thalamocortical network in the parkinsonian brain.

In summary, the loss of DA in the striatum triggers numerous synaptic and cellular alterations in the basal ganglia nuclei, which are believed to underlie the pathological pattern of activity throughout the cortico-basal ganglia-thalamocortical network and eventually contribute to the devastating motor symptoms of PD. The disruption of an abnormal pattern of activity within the network is proposed to be a common mechanism underlying the therapeutic effects of symptomatic treatments. It is worth noting that a reduction in striatal DA levels and changes in striatal SPNs activity are responsible for all adaptive changes in downstream targets, such as those in the STN and SNr. For example, the upregulation of iSPNs activity using chemogenetic tools in mice with normal DA levels triggers similar synaptic and cellular adaptations in the STN and impairs the plasticity associated with DA depletion in 6-OHDA-lesioned models of PD [69]. Moreover, SNr GABAergic projection neurons also exhibit adaptive changes in neurotoxin-based models, and the extent of these adaptations correlates with the amount of striatal DA [75]. However, it remains uncertain whether, as the dopamine level drops, alterations in striatal dSPNs, iSPNs, or both are critical for triggering network-level alterations within the cortico-basal ganglia-thalamocortical network.

CONCLUSION

The loss of DA neuromodulation in the basal ganglia induces numerous adaptive changes at the molecular, cellular, and circuit levels, ultimately leading to the manifestation of a pathological pattern of activity in the parkinsonian brain. Recent advances in neurotechnology for cell labeling and neural activity monitoring have provided the field with unique opportunities to evaluate adaptive changes in the parkinsonian brain in a cell-type- and synapse-defined way, which will give rise to critical information that is required to advance our understanding of the cellular and circuit bases of PD pathophysiology. Once again, most of our current knowledge regarding adaptive changes in the parkinsonian brain comes from postmortem analysis of brain tissues from PD patients or neurotoxin-based animal models of end-stage PD. We have limited information on how the brain adapts to gradual DA degeneration, such as that which in PD, and this is a basic and critical question that needs to be addressed in the next decade. The development and characterization of genetic and α-synuclein-based progressive models of PD [76, 77] represent a great opportunity for the field to analyze brain adaptations at the cellular and circuit levels as the disease progresses. With this information, we will be able to causally link changes in the brain with the critical pathophysiological mechanisms that drive PD symptoms.

ADDITIONAL INFORMATION

Competing interests: The author declare no competing interests.

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