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Striatal plasticity and medium spiny neuron dendritic remodeling in parkinsonism

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Abstract

Current approaches to Parkinson's Disease (PD) are largely based on our current understanding of the mechanisms that contribute to the death of nigrostriatal dopamine neurons. However, our understanding of the consequences of the loss of dopamine on the striatal target cells of nigrostriatal neurons is much less advanced. In particular, the compensatory changes that occur in striatal medium spiny neurons (MSNs) that have lost their normal dopamine input remains poorly understood. The compensatory changes may have either positive or negative effects. Among the alterations that occur in striatal cells of the dopamine-denervated striatum are dystrophic changes in the dendrites of MSNs, with a loss of dendritic length and dendritic spine number. Dendritic spines are the targets of convergent nigrostriatal dopamine and corticostriatal glutamate axons, and integrate these convergent signals to determine the nature of striatal output. The loss of these spines in the dopamine-denervated state may protect the MSN from overt excitotoxic death, but at the price of compromising MSN function. The loss of dendritic spines is thought be responsible for the gradual decrease in levodopa efficacy in late-stage PD, suggesting that therapeutic interventions need to be developed that target key downstream signaling complexes in medium spiny neurons.

Keywords

Parkinson's disease; Synaptic plasticity; Dendritic remodeling; Medium spiny neurons; CaMKII; F-actin

1. Introduction

Degeneration of nigrostriatal dopamine neurons and the resultant decrease in striatal dopamine concentrations give rise to the motor signs and symptoms of Parkinson's disease.

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Conflict of Interest statement

The authors have declared no conflicts of interest for the topics addressed in this manuscript. AYD is a consultant for Eli Lilly and Co on other topics.

Accordingly, research efforts have largely, and logically, focused attention on defining factors that result in degeneration of nigrostriatal dopamine neurons, and in elucidating the effects of dopamine replacement treatments on dopamine neurons. In contrast, relatively little attention has been oriented toward the striatal neurons that receive a dopaminergic input, and defining how these neurons are impacted by dopamine loss.

2. Morphological changes in the dopamine-denervated striatum

2.1. Medium spiny neurons

The medium spiny neuron (MSN) is the target of the dopamine innervation of the striatum, and comprise more than 90% of striatal neurons. These MSNs are, as their name suggests, of medium size and have radially projecting dendrites that are densely studded with dendritic spines. These projection neurons of the striatum use GABA as a transmitter, with two different peptide transmitters being co-localized to define two sets of MSNs. The first of these groups of MSNs project directly to the substantia nigra (SN), express the tachykinin peptide substance P, and express the D1 dopamine receptor. The other group of MSNs projects to the globus pallidus (neurons of which in turn project to the SN and motor thalamus), express the peptide leu-enkephalin as a co-transmitter with GABA, and express and are regulated by the D2 dopamine receptor.

Electron microscopic studies have found that the synapse between the dopamine axon innervating the striatum and the dendrite is precisely arranged, with most dopamine axons forming symmetric synapses onto the neck of dendritic spines [1]. In addition, there is a third synaptic partner, an excitatory glutamatergic axon from cortical neurons that contacts the head of the spine. Thus, there is a triad consisting of a dopamine axon that synapses with the dendritic spine neck and a glutamate axon that contacts the spine head. This synaptic architecture suggests that one of the functions of dopamine is to modulate the effects of excitatory corticostriatal glutamatergic drive over MSNs.

2.2. Consequences of dopamine denervation of striatal neurons

In the dopamine-denervated striatum MSNs exhibit a hyperexitability [2,3], consistent with an increased glutamatergic drive from corticostriatal neurons. A variety of consequences ensue. Among these are the potential for changes in the structure of dendritic spines, the morphological substrate for cortical and dopamine inputs onto MSNs. Dendritic spines, as Francis Crick elegantly phrased it [4], twitch. Although Cajal commented on the dynamics of dendrites and dendritic spines in the late 19th century (see [5]), almost a hundred years ensued before we appreciated (yet again) his prescience. Today, changes in dendritic spines, with the resultant alterations in excitatory neuronal transmission and the functional output of affected neurons, are viewed as key changes underlying a variety of neuropsychiatric disorders.

Both post-mortem studies of idiopathic PD and laboratory studies of animal models of parkinsonism have found that striatal dopamine depletion results in dystrophic changes in the dendrites of striatal MSNs [3,6–8]. The morphological changes in MSNs include decreases in dendritic length, dendritic spine density, and total number of dendritic spines. In addition, there are changes in the shapes of the remaining dendritic spines. Because dendritic

spines are physiologically independent compartments, changes in intracellular calcium levels determine both spine stability and the shape of spines [9].

The decrease in MSN dendritic spines in the dopamine-denervated striatum is not a consequence of aging. Thus, although the MSNs of one-year old rats have significantly fewer dendritic spines, there is a further reduction in animals maintained for one year after dopamine denervation, with the relative (percent) decrease in spine density being the same in those animals examined three weeks after striatal dopamine denervation and those examined one year later (unpublished data).

2.3. Mechanism of MSN dendritic remodeling

Some of the mechanisms that subserve dendritic changes in striatal MSNs in PD have become clear over the past few years, including loss of dopamine as an initiating (but not continued expression) event, and the contribution of changes in intracellular Ca^{2+} levels. Available information suggests key roles in several areas, but the precise identities of these contributing factors are not yet known.

First, it is clear that dopamine depletion is the initiating event: MSN spine loss is seen in postmortem studies of PD, and in animals treated with 6-hydroxydopamine or reserpine to deplete striatal dopamine stores, as well as in animals in which dopamine signaling has been disrupted by chronic treatment with the D_2 receptor antagonist haloperidol [3, 6–8,10]. The latter finding, and the observation that MSNs of mice genetically lacking the D_2 dopamine receptor suffer from a loss of dendritic spines (unpublished observation), suggests that spine loss might be confined to MSNs that normally express the D_2 receptor. This is indeed the case: a recent study that monitored the expression of markers of the direct and indirect MSN found that only the D_2 receptor-expressing MSNs, which contribute to the indirect pathway, but not the MSNs that comprise the indirect pathway, show a loss of dendritic spines in response to dopamine depletion [3].

We discussed above how the dopamine axon that synapses with the dendritic spine of an MSN is part of a triad of structures, the third being an excitatory glutamatergic input from the cortex. A D_2-like heteroceptor localized to the terminals of corticostriatal axons regulates release of glutamate from these striatal inputs [11]. Accordingly, the loss of the striatal dopamine innervation is accompanied by a removal of the dopamine D_2-mediated inhibition on glutamate release. This contributes to the hyperexcitability of the MSN in the dopamine-denervated striatum. We recently used triple organotypic slice cultures comprised of the striatum, substantia nigra, and cortex, and found that we could recapitulate the dendritic spine loss observed *in vivo* in the dopamine-denervated striatum *in vitro*. More importantly, if the cortex was removed from the cultures, dopamine denervation-induced dendritic spine loss was completely blocked [12], consistent with a crucial and necessary role for increased corticostriatal glutamatergic drive.

The observation that decortication prevents dendritic spine loss suggests that an increase in intracellular calcium levels may contribute to the loss of spines. This is consistent with several studies which have found that a rapid increase in intracellular Ca^{2+} levels leads to dendritic spine changes [9,13]. The increase in calcium may arise from glutamate acting on

NMDA receptors to increase intracellular Ca^{2+}, or through a change in voltage-gated calcium channels.

D_2 receptors also regulate calcium entry into MSNs through voltage-gated calcium channels (VGCC). Thus, D_2 tonically inhibits a $Ca_V1.3$ calcium channel expressed in MSNs and thereby reduces excitability of the neuron [14]. Recently, we collaborated with Surmeier and colleagues and found that systemic administration of nimodipine, a VGCC antagonist, prevented dopamine-depletion induced dendritic spine loss, and that spine loss was not seen in mutant mice lacking the $Ca_V1.3$ gene [3].

These data cumulative suggest that decreasing the excitability of MSNs by reducing the surge in intracellular Ca^{2+} that accompanies dopamine depletion is an effective strategy for mitigating the MSN spine loss seen in parkinsonism.

2.4. The clinical relevance of MSN dendritic spine loss and treatment options

We have not discussed the clinical implications for striatal neuron dendritic spine loss in PD. There has been a widespread suggestion that in late-stage PD there is a diminished response to levodopa (see [15]). It has been somewhat difficult to clearly define a decreased responsiveness to dopamine replacement therapy because dyskinesias present an upper limit on the levodopa (or agonist) dose. Nonetheless, it is clear that there is a dose escalation without a comparable therapeutic benefit, consistent with a diminished loss of responsive to levodopa.

The dendritic spine of MSNs is the site of integration of several key inputs to the striatal neuron that cooperatively regulate the output of the striatum. Dopamine and glutamate axons synapse onto the dendritic spine of the MSN, which in turn expresses the appropriate dopamine and glutamate receptors poised to respond to dopamine and glutamate. Early in PD, including in never-medicated patients, there is an increase in the density (binding potential) of striatal D_2 receptors, consistent with an denervation-induced upregulation of the dopamine receptor. However, as spine number continues to drop, it is reasonable to expect that there would be a limit on the capacity of the MSN to compensate for the loss of dopamine by increasing dopamine receptor number, culminating in the difficulties in effectively treating patients with PD of long duration. As clinical treatment improves in many realms, with an increase in the expected life span of PD patients, a means of countering the decreased responsiveness to dopamine replacement will represent a very significant advance.

We have not yet mentioned the effect of levodopa on dendritic spine loss. We have found that high-dose levodopa treatment does not restore dendritic spine density to control levels in rats with striatal dopamine denervation (unpublished observation). This is consistent with our and other post-mortem studies of PD [6,7], in which marked dendritic spine loss was present despite all patients having received levodopa or a dopamine agonist. Thus, spine loss, at least once established, is not reversible by dopamine replacement. Moreover, as MSN dendritic spine loss is also seen in animals never treated with levodopa [8], there does not appear to be a direct association between spine loss and dyskinesias, but rather a link between spine loss and the motor symptoms of PD.

The failure of levodopa to increase spine density toward control levels is consistent with the concept that once established by dopamine denervation, non-dopaminergic therapeutics will be required to fully restore function. Glutamate receptor antagonists would seem to be logical choices because the increase in glutamatergic drive appears to be responsible, at least in part, for spine loss; however, the few clinical trials to date of glutamate antagonists have not been encouraging. Certain VGCC antagonists might also be a useful approach. The piperazine VGCC antagonists, such as flunarizine and cinnarizine, are also D_2 receptor antagonists, and thus have been reported to cause parkinsonism. However, most VCGG antagonists do not cause parkinsonism, and a recent epidemiological study indicated that calcium channel blockers do not increase the risk of developing PD [15]. However, the hypotensive actions of VGCCs are a potential concern for using these drugs in PD, in which many patients already have autonomic dysfunction. Interestingly, the VGCC antagonists do not appear to cause a decrease in blood pressure in normotensive subjects, suggesting that the use of these compounds may not be contraindicated in clinical practice.

Ultimately, the development of novel non-dopaminergic theapeutic strategies will likely depend on rationale identification of downstream targets of the D_2 receptors. This daunting task requires a clear understanding of the intersection of dopamine and glutamatergic signaling at the MSN dendritic spine. This topic is discussed in much greater detail below.

3. Alterations in signaling in the dendritic spine of dopamine-denervated striatal cells

As noted above, a key determinant of the MSN spine loss seen in response to dopamine denervation is a rise in intracellular Ca^{2+} levels. Increases in intracellaular Ca^{2+} lead to a complex array of changes in structural and signaling proteins. We will discuss Ca^{2+}-dependent modulation of downstream effectors and structural proteins in the dendritic spine.

Changes in intracellular Ca^{2+} are sensed by calmodulin, which binds four Ca^{2+} ions and then regulates other proteins. Among these other proteins are Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) and the Ca^{2+}/calmodulin-dependent protein phosphatase 2B, both of which have important roles in dendritic spines. Ca^{2+} has a pre-eminent role in spine signaling because Ca^{2+}/calmodulin signaling cross-talks to other second messengers (e.g., cAMP, lipids), small G proteins, and MAP kinases (reviewed in [16]).

3.1. Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII)

Mammals express more than 20 isoforms of CaMKII, which are derived from four genes. Despite the complexity of CaMKII, in the adult forebrain there is an approximately 4:1 ratio of CaMKIIα to CaMKIIβ splice variants, with little CaMKIIγ or CaMKIIδ.

The phosphorylation of CaMKII integrates information conveyed by changes in the frequency, duration, and amplitude of transient Ca^{2+} signals [17]. Under basal conditions, when Ca^{2+} and calmodulin are not present, CaMKII is inactive. Binding of Ca^{2+}/calmodulin to adjacent subunits in the dodecameric CaMKII holoenzyme stimulates inter-subunit autophosphorylation at Thr^{286}, resulting in Ca^{2+}-independent (autonomous) CaMKII activity, which serves as a molecular memory of transient Ca^{2+} signals. When Ca^{2+}/

calmodulin is not bound, CaMKII is autophosphorylated at Thr^{305} or Thr^{306}, inhibiting signaling by blocking the subsequent binding of Ca^{2+}/calmodulin.

In situ CaMKII autophosphorylation depends on the balance between Ca^{2+}/calmodulin stimulation and the opposing phosphatases. Phospho-Thr^{286} in CaMKII is de-phosphorylated by several protein phosphatases, including PP1, PP2A and PP2C [18]; dephosphorylation of phospho-Thr^{305}/Thr^{306} is not well understood. Although there is no evidence for a direct role of PP2B (also known as calcineurin), PP2B may indirectly modulate CaMKII dephosphorylation via regulation of PP1 (see below).

CaMKII holoenzymes are inherently soluble, yet CaMKII is highly abundant in isolated postsynaptic densities (PSDs). Detailed microscopic studies showed that activated CaMKII translocates from cytosol to the postsynaptic densities (PSDs) in dendritic spines. The localization of CaMKII to the PSD is determined by phosphorylation of the enzyme, such that Thr^{286} autophosphorylation stabilizes CaMKII localization to PSDs while phosphorylation at Thr^{305}/Thr^{306} promotes CaMKII dissociation. Autophosphorylation at Thr^{253} may stabilize the association with PSDs in the absence of Thr^{286} autophosphorylation, with PSDs with abundant CaMKII representing highly active, “potentiated” synapses.

Certain CaMKII-associated proteins (CaMKAPs) have been identified, and may cooperatively mediate dynamic targeting of CaMKII to PSDs and other subcellular structures (reviewed in [19]). For example, interactions of activated CaMKII with the NMDA receptor subunit NR2B can mediate activation-dependent CaMKII translocation, but binding to NR2B is relatively insensitive to Thr^{306}/Thr^{306} autophosphorylation. Rather, Thr^{305}/Thr^{306} autophosphorylation disrupts interactions of CaMKII with α-actinin [20]. In contrast, binding of CaMKII with densin-180 is relatively insensitive to CaMKII activation or autophosphorylation.

Perhaps the best characterized synaptic substrate for CaMKII is the GluR1 subunit of AMPA-type glutamate receptors. CaMKII (and PKC) phosphorylates Ser^{831} to increase conductance of AMPARs and drives synaptic insertion of new GluR1 subunits. These actions of CaMKII play a role in hippocampal LTP induction, but the role of CaMKII modulation of GluR1 in striatum is poorly understood.

Most studies of the regulation of CaMKII have been performed in the hippocampus. While it is unclear if the data from these hippocampal studies uniformly generalize to striatal MSNs, the data derived from hippocampal studies are nonetheless valuable in directing attention to key regulatory steps. In hippocampal neurons an increase in cytosolic Ca^{2+} via any mechanism will lead to some degree of CaMKII autophosphorylation. Recent studies found that binding of CaMKII to CaMKAPs and the PSD modulates the sensitivity to Ca^{2+} mobilization and the downstream signaling specificity [21]. Indeed, association of CaMKII with CaMKAPs influences CaMKII activity *in vitro* and in intact cells. In addition, association of CaMKII with PSDs appears to modulate the availability of Thr^{286} to different phosphatases, with PP1 playing a dominant role within the PSD [18]. This results in PP1

exerting a “gate-keeping” role over CaMKII. Thus, PP1 inhibition is required for sustained CaMKII activation and induction of LTP.

PP2B is unusual among mammalian protein serine/threonine phosphatases because it is directly regulated by a second messenger and has a relatively restricted substrate specificity. It is typically found in the postsynaptic density, where it is associated with AKAP79/150, an anchoring protein for cAMP-dependent protein kinases. The association of AKAP79/150 with SAP97 targets PKA and PP2B to regulate AMPAR GluR1 subunits. In addition, PP2B is closely associated with IP_3 and ryanodine receptors via its interactions with immunophilin proteins, presumably facilitating efficient regulation of PP2B by Ca^{2+} release from intracellular stores.

The best established PP2B substrate is DARPP-32, a protein that regulates PP1 and is highly expressed in the striatum. PKA phosphorylates DARPP-32 at the Thr^{34} residue in response to D_1 dopamine receptors activation. The Thr^{34} phosphorylation of DARPP-32 is antagonized by PP2B-mediated dephosphorylation. Thr^{34}-phosphorylated DARPP-32 is a potent PP1 inhibitor. Thus, D_1 dopamine signaling inhibits PP1 by increasing Thr^{34} phosphorylation of DARPP-32, and stimulation of PP2B by activation of NMDA or D_2 receptors activates PP1 by dephosphorylating Thr^{34}. Modulation of PP1 via DARPP-32, or its homolog inhibitor-1, plays a major role in mediating the synaptic and behavioral effects of dopamine and glutamate in the striatum (reviewed in [22]).

Ca^{2+}-dependent dephosphorylation of intact cells may be a direct consequence of increased PP2B activity or due to activation of PP1 via PP2B dephosphorylation of DARPP-32 (or inhibitor-1). For example, dephosphorylation of AMPA receptor GluR1 subunits has been attributed to direct actions of PP2B or indirect actions of PP2B via PP1, perhaps depending on the specific neuronal and signaling context. Synaptic targeting of PP1 by spinophilin and neurabin is important for normal regulation of AMPAR and NMDAR phosphorylation. Genetic manipulations of PP2B activity and DARPP-32 disrupt normal synaptic plasticity and behaviors in multiple brain regions, including the striatum (see below).

3.2. Regulation of F-actin in spines

Ca^{2+} modulation of PP2B activity plays a key role in regulating the dynamics of the cytoskeletal protein F-actin [23]. In addition, spinophilin and neurabin are F-actin-binding proteins that specifically target the PP1γ1 isoform and several rac and rho-specific modulators to the F-actin cytoskeleton in dendrites. Spinophilin knockout mice develop spines on striatal MSNs prematurely and exhibit increased dendritic spine densities early in postnatal development. CaMKII also modulates dendritic morphology. Early studies suggested that dendritic arbor structure is stabilized by CaMKII [24]. and CaMKII-dependent modulation of transcription is an important determinant of dendritic morphogenesis [25]. Morever, the interaction of CaMKIIβ with F-actin is important for maintenance of dendritic spines. Recent studies found that CaMKIIα can assemble multiprotein complexes containing NR2B, densin-180, and α-actinin *in vitro* [26]. Indeed, CaMKII is precisely arrayed on the intracellular surface of PSDs, and activation and/or overexpression of CaMKIIα can induce morphological changes in spines, suggesting a structural role for CaMKII. These observations illustrate the complexities of Ca^{2+}-dependent

mechanisms for regulating dendritic spine morphology. Again, much of this information has been gleaned from studies of hippocampal pyramidal cells, and the precise contributions to striatal MSNs, while no doubt sharing many features, will also probably differ in certain key aspects.

3.3. Impact of dopamine depletion on striatal signaling

The loss of MSN dendritic spines in response to striatal dopamine denervation is due, in part, to Ca^{2+} influx via $Ca_V1.3$ L-type voltage-gated calcium [3]. As note earlier, Ca^{2+} influx through the NMDA receptor is also involved. Thus, a rapid surge in intracellular Ca^{2+} to sufficient levels results in dystrophic changes in dendrites, including spine loss. Because CaMKII is key integrator of changes in intraspinous Ca^{2+}, one would expect that striatal dopamine depletion elicits changes in CaMKII. This is indeed the case: dopamine depletion increases CaMKII autophosphorylation at Thr^{286}, as well as CaMKII association with NMDA receptors, but lower levels of CaMKII are associated with PSD-enriched subcellular fractions [27,28]. In addition, biochemical studies have revealed defects in the expression, phosphorylation, and subcellular distribution of AMPA and NMDA glutamate receptor subunits [29], which are downstream targets of CaMKII.

The increase in levels of phosphoThr^{286} CaMKII in response to striatal dopamine depletion suggests implies that striatal CaMKII is more active in the parkinsonian striatum. However, GluR1 phosphorylation was unchanged during the first month after dopamine depletion. Although the progression of aging in dopamine-depleted animals resulting in no further changes in Thr^{286} phosphorylation, over an 18-month period a progressive increase in GluR1 phosphorylation at Ser^{831}, but not Ser^{845}, was observed [27]. These data suggest complex interactions between dopamine depletion and aging result in evolving changes in striatal signaling pathways.

What is the effect of dopamine-replacement in the striatum of parkinsonian rodents on CaMKII? We found that chronic levodopa treatment reversed the increase in CaMKII autophosphorylation in the dopamine-denervated striatum, without affecting CaMKII in the intact striatum. Thus, it is clear that dopamine depletion induces substantial changes in the overall signaling environment. Importantly, CaMKII inhibition has been reported to normalize behavioral defects and changes in striatal synaptic plasticity in dopamine-depleted animals [28]. Strikingly, however, levodopa treatment did not reverse the decrease in MSN dendritic spine density seen in the dopamine-denervated striatum. Thus, it appears that once spine loss has become established interventions that target the dopamine receptor are ineffective, but that interventions downstream of the dopamine receptor and CaMKII may play an important role. Although levodopa treatment did not reverse the spine loss in the dopamine-denervated striatum, it does reverse some of the associated motor effects. Taken together, these data suggest that CaMKII may be a viable therapeutic target to limit side effects associated with prolonged levodopa treatment.

4. Synaptic plasticity in the dopamine-denervated striatum

Changes in dendritic spine number and morphology are associated with long-term alterations in the efficacy of excitatory transmission. For example, synaptic plasticity at

glutamatergic synapses has long been postulated to play roles in hippocampal-based long-term memory [30]. In recent years, synaptic plasticity at corticostriatal synapses has been suggested to play a key role in habit-based learning [31]. Moreover, various forms of glutamatergic synaptic plasticity are altered in the dopamine-denervated striatum [32,33], paralleling the decrease in MSN dendritic spine density. We have examined the structural and biochemical alterations in MSNs that occur in response to dopamine denervation, and will now explore the physiological consequences that are associated with a decrease in striatal dopamine.

4.1. Metabotropic glutamate receptor/endocannabinoid long-term depression

The two major forms of glutamatergic synaptic plasticity that have been studied at corticostriatal synapses are endocannabinoid-dependent long-term depression (LTD) of synaptic transmission, and NMDA receptor-dependent long-term potentiation (LTP). In contrast to NMDA receptor-dependent LTD, which is elicited by weak patterns of afferent activity, endocannabinoid LTD at corticostriatal terminals can be elicited by high-frequency tetanization paradigms that typically elicit NMDA receptor-dependent LTP in other brain regions [34]. A large literature indicates that this LTD is induced postsynaptically, through the recruitment of group I metabotropic glutamate receptors (mGluRs) and L-type calcium channels [35]. The resultant rise in postsynaptic calcium levels results in the release of endocannabinoids and subsequent activation of presynaptic CB1 receptors to persistently decrease transmitter release [36]. Surprisingly little is known of the specific identity of the calcium-activated proteins involved in this form of synaptic plasticity, although in other systems both calcineurin [37] and CaMKIIα [38] have been implicated in different LTD mechanisms.

4.2. NMDA receptor-dependent long term potentiation

LTP in the striatum shares at least some properties with LTP in the hippocampus, in that it is NMDA receptor dependent. However, basic questions currently remain unanswered, for example the relative contribution of CaMKIIα and the degree to which this LTP is constrained by calcineurin. Further, in contrast to LTP in the hippocampus, which is robustly induced under physiological conditions, LTP in the striatal slice is most commonly observed only under non-physiological conditions such as in the absence of extracellular Mg^{2+} [3], unless induced by chemical means or in striatal slices from very young rodents [39]. Curiously, however, LTP is robustly observed in *in vivo* striatal recordings, suggesting that extrinsic afferents may play a critical maintenance role [40].

4.3. Parkinson's Disease and striatal synaptic plasticity

In most brain areas, such as the hippocampus, glutamatergic LTP and LTD are typically considered to be homosynaptic processes that are induced and maintained solely through glutamatergic transmission. This does not appear to be case in the striatum, where pharmacological and lesion studies indicate that striatal LTP and LTD depend on intact dopaminergic signaling, indicating a heterosynaptic component to these forms of plasticity. Thus, treatment of animals with dopamine receptor antagonists and studies in dopamine receptor null mutant mice has indicated a role for D_2 dopamine receptors in striatal LTD and D_1 receptors in striatal LTP [32]. Moreover, lesions disrupting the striatal dopamine

innervation ablate both high-frequency stimulus-induced LTP and LTD [32]. However, more recent data suggests that this dopaminergic control of striatal plasticity may be more modulation than mediation. First, a form of LTP elicited chemically by application of the potassium channel blocker TEA can induce LTP in striatal slices taken from rats with striatal dopamine lesions [41]. Further, recent studies have suggested that the dopamine control of LTD in the striatum can be surpassed via manipulation of cholinergic transmission in the striatum, suggesting that the role of dopamine may be more at the level of modulation of cholinergic interneurons rather than directly on glutamatergic plasticity *per se* [35].

Recent evidence suggests that dopaminergic control of striatal synaptic plasticity is an acute process. Calabresi and associates demonstrated that *in vivo* dopamine replacement therapy could rapidly “rescue” striatal LTP [42]. Interestingly, they went on to show that dopamine replacement therapy could induce motor disturbances in rodents reminiscent of those observed as dyskinesias in Parkinson’s patients. In slices taken from naive rats, or from levodopa-treated rats that did not exhibit motor disturbances, a low-frequency stimulus applied to the striatal slice after the high-frequency stimulus could “depotentiate” the LTP that had been elicited. In other brain regions, this depotentiation depends on Ser/Thr phosphatase activation, including PP1 and calcineurin [43]. In contrast, in slices taken from dopamine replacement rats that exhibited motor disturbances, low-frequency stimulation does not produce depotentiation [42]. This raises the possibility that phosphatase signaling has been disrupted.

4.4. New directions in the study of synaptic plasticity in the dorsal striatum

Until recently, a major drawback in the study of synaptic physiology of medium spiny neurons was the inability to discriminate between striatonigral (direct pathway) or striatopallidal (indirect pathway) MSNs. The development of bacterial artificial chromosome (Bac) transgenic mice has provided an approach to identify neurons. The GENSAT consortium has generated a number of Bac-transgenic mice expressing enhanced green fluorescent protein (EGFP) under the direction of promoters of genes of interest [44,45]. For example, D1- and D2-Bac transgenics express EGFP under the D1 and D2 receptor promoters, respectively, marking the direct and indirect pathways. Other Bac transgenics are also useful in this regard, including the M4 muscarinic receptor Bac for the direct pathway and a preproenkephalin Bac (PENK) for the indirect pathway.

Using mice expressing EGFP in D_1 (direct) and D_2 (indirect) MSNs, Surmeier and colleagues have shown that endocannabinoid LTD can be elicited on glutamate afferents to both populations of neurons [35], but that dopamine depletion produces a large loss of glutamate synapses and spines on indirect pathway but not direct pathway neurons [3]. In contrast, Krietzer and Malenka, using the M4 and D2 Bac transgenics, report that LTD only occurs on indirect pathway neurons [46]. The reason for this discrepancy is not clear. As with any transgenic approach, care must be taken in interpretation of data obtained from Bac transgenic mice. In particular, the high fidelity of expression pattern allowed by the Bac transgenic occurs in large part through the very large piece of genetic material that contains the promoter of interest. Often, this can be so large that it includes additional genes, resulting in the unintended overexpression of other gene products. Another potential

problem of Bac transgenics is that the random insertion point in the genome may on its own generate a phenotype. The use of multiple transgenic lines with different integration sites has been an effective strategy for avoiding this complication. Further, the use of more than one Bac-transgene to identify a population of cells, such as the D1 and M4, decreases the likelihood that "hitchhiker" genes in one of the Bacs will contribute to observed phenotypes.

5. Conclusions

It is now clear that there are structural changes in the striatum in PD. These changes are more subtle than those seen in other brain areas, such as the overt degeneration of substantia nigra dopamine neurons. However, the dystrophic changes in the dendrites of MSNs undermine the structural basis of synaptic communication, including disrupting signaling through extended corticostriatofugal pathways. Given the convergent arrival of dopamine and glutamate inputs to a common MSN spine, a complete understanding of the dynamic regulation of the cognate receptors for these transmitters and their downstream signaling targets is necessary will be required to significantly advance in our ability to treat PD.

Parkinson's disease patients initially respond very well to dopamine replacement, but over the ensuing years complications and side effects arise. Current treatment approaches have limited efficacy in late-stage PD. This may be due to a progressive loss of dendritic spines of the striatal neurons, on which dopamine receptors reside, until such a time as the capacity of the MSN to compensate for the loss of dopamine by increasing D_2 receptor expression is overwhelmed and dopamine replacement strategies become less effective. Studies aimed at uncovering the mechanisms of dendritic remodeling in the striatum and the interaction of these mechanisms with aging may open new and better treatment strategies for Parkinson's disease.

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References

1. Wickens, JR.; Arbuthnott, GW. Structural and functional interactions in the striatum at the receptor level. In: Dunnett, SB.; Bentivoglio, M.; Bjorklund, A.; Hokfelt, T., editors. Dopamine, vol. 21 of Handbook of Chemical Neuroanatomy. Amsterdam: Elsevier; 2005. p. 199-236.
2. Cepeda C, Hurst RS, Altemus KL, Flores-Hernandez J, Calvert CR, Jokel ES, et al. Facilitated glutamatergic transmission in the striatum of D2 dopamine receptor-deficient mice. J Neurophysiol. 1998; 85:659–70. [PubMed: 11160501]
3. Day M, Wang Z, Ding J, An X, Ingham CA, Shering AF, et al. Selective elimination of glutamatergic synapses on striatopallidal neurons in Parkinson disease models. Nat Neurosci. 2006; 9:251–9. [PubMed: 16415865]
4. Crick F. Do spines twitch? Trends Neurosci. 1984; 5:44–6.
5. DeFelipe J. Brain plasticity and mental processes: Cajal again. Nat Rev Neurosci. 2006; 7:811–7. [PubMed: 16988656]
6. Zaja-Milatovic S, Milatovic D, Schantz AM, Zhang J, Montine KS, Samii A, et al. Dendritic degeneration in neostriatal medium spiny neurons in Parkinson disease. Neurol. 2005; 64:545–7.

7. Stephens B, Mueller AJ, Shering AF, Hood SH, Taggart P, Arbuthnott GW, et al. Evidence of a breakdown of corticostriatal connections in Parkinson's disease. Neuroscience. 2005; 132:741–54. [PubMed: 15837135]
8. Ingham CA, Hood SH, Arbuthnott GW. Spine density on neostriatal neurones changes with 6-hydroxydopamine lesions and with age. Brain Res. 1989; 503:334–8. [PubMed: 2514009]
9. Segal M, Andersen P. Dendritic spines shaped by synaptic activity. Curr Opin Neurobiol. 2000; 10:582–6. [PubMed: 11084320]
10. Rodriguez JJ, Pickel VM. Enhancement of N-methyl-D-aspartate (NMDA) immunoreactivity in residual dendritic spines in the caudate-putamen nucleus after chronic haloperidol administration. Synapse. 1999; 33:289–303. [PubMed: 10421710]
11. Bamford NS, Robinson S, Palmiter RD, Joyce JA, Moore C, Meshul CK. Dopamine modulates release from corticostriatal terminals. J Neurosci. 2004; 43:9541–52. [PubMed: 15509741]
12. Neely MD, Schmidt DE, Deutch AY. Cortical regulation of dopamine depletion-induced dendritic spine loss in striatal medium spiny neurons. Neurosci. In Press. 10.1016/j.neuroscience.2007.06.044
13. Segal M. Dendritic spines for neuroprotection: a hypothesis. Trends Neurosci. 1005; 18:468–471. [PubMed: 8592749]
14. Hernandez-Lopez S, Tkatch T, Perez-Garci E, Galarraga E, Bargas J, Hamm H, et al. D_2 dopamine receptors in striatal medium spiny neurons reduce L-type Ca^{2+} currents and excitability via a novel PLC[beta]1-IP3-calcineurin-signaling cascade. Neurosci. 2000; 20:8987–95.
15. Ton TG, Heckbert SR, Longstreth WT Jr, Rossing MA, Kukull WA, Franklin GM, et al. Calcium channel blockers and beta-blockers in relation to Parkinson's disease. Parkinsonism Relat Disord. 2007; 13:165–9. [PubMed: 17055323]
16. Xia Z, Storm DR. The role of calmodulin as a signal integrator for synaptic plasticity. Nat Rev Neurosci. 2005; 6:267–76. [PubMed: 15803158]
17. DeKoninck P, Schulman H. Sensitivity of CaM kinase II to the frequency of Ca^{2+} oscillations. Science. 1998; 279:227–30. [PubMed: 9422695]
18. Strack S, Barban MA, Wadzinski BE, Colbran RJ. Differential inactivation of postsynaptic density-associated and soluble Ca^{2+}/calmodulin-dependent protein kinase II by protein phosphatases 1 and 2A. J Neurochem. 1997; 68:2119–28. [PubMed: 9109540]
19. Colbran RJ. Targeting of calcium/calmodulin-dependent protein kinase II. Biochem J. 2004; 378:1–16. [PubMed: 14653781]
20. Robison AJ, Bartlett RK, Bass MA, Colbran RJ. Differential modulation of Ca2+/calmodulin-dependent protein kinase II activity by regulated interactions with N-methyl-D-aspartate receptor NR2B subunits and alpha-actinin. J Biol Chem. 2005; 280:39316–23. [PubMed: 16172120]
21. Tsui J, Inagaki M, Schulman H. Calcium/calmodulin-dependent protein kinase II (CaMKII) localization acts in concert with substrate targeting to create spatial restriction for phosphorylation. J Biol Chem. 2005; 280:9210–16. [PubMed: 15582994]
22. Svenningsson P, Nishi A, Fisone G, Girault JA, Nairn AC, Greengard P. DARPP-32: An integrator of neurotransmission. Ann Rev Pharmacol Toxicol. 2004; 44:269–96. [PubMed: 14744247]
23. Halpain S, Hipolito A, Saffer L. Regulation of F-actin stability in dendritic spines by glutamate receptors and calcineurin. J Neurosci. 1998; 18:9835–44. [PubMed: 9822742]
24. Wu GY, Cline HT. Stabilization of dendritic arbor structure in vivo by CaMKII. Science. 1998; 279:222–6. [PubMed: 9422694]
25. Gaudilliere B, Konishi Y, de la Iglesia N, Yao G, Bonni A. A CaMKII-NeuroD signaling pathway specifies dendritic morphogenesis. Neuron. 2004; 41:229–41. [PubMed: 14741104]
26. Robison AJ, Bass MA, Jiao Y, MacMillan LB, Carmody LC, Bartlett RK, et al. Multivalent interactions of calcium/calmodulin-dependent protein kinase II with the postsynaptic density proteins NR2B, densin-180, and alpha-actinin-2. J Biol Chem. 2005; 280:35329–36. [PubMed: 16120608]
27. Brown AM, Deutch AY, Colbran RJ. Dopamine depletion alters phosphorylation of striatal proteins in a model of parkinsonism. Eur J Neurosci. 2005; 22:247–56. [PubMed: 16029214]

28. Picconi B, Gardoni F, Centzone D, Mauceri D, Cenci MA, Bernardi G, et al. Abnormal Ca^{2+}-calmodulin-dependent protein kinase II function mediates synaptic and motor deficits in experimental Parkinsonism. J Neurosci. 2004; 24:5283–91. [PubMed: 15190099]
29. Oh JD, Vaughan CL, Chase TN. Effect of dopamine denervation and dopamine agonist administration on serine phosphorylation of striatal NMDA receptor subunits. Brain Res. 1999; 821:433–42. [PubMed: 10064831]
30. Whitlock JR, Heynen AJ, Shuler MG, Bear MF. Learning induces long-term potentiation in the hippocampus. Science. 2006; 313:1093–97. [PubMed: 16931756]
31. Yin HH, Knowlton BJ. The role of the basal ganglia in habit formation. Nat Rev Neurosci. 2006; 7:464–76. [PubMed: 16715055]
32. Centonze D, Picconi B, Gubellini P, Bernardi G, Calabresi P. Dopaminergic control of synaptic plasticity in the dorsal striatum. Eur J Neurosci. 2001; 13:1071–77. [PubMed: 11285003]
33. Tang K, Low MJ, Grandy DK, Lovinger DM. Dopamine-dependent synaptic plasticity in striatum during in vivo development. Proc Natl Acad Sci USA. 2001; 98:1255–60. [PubMed: 11158626]
34. Lovinger DM, Tyler EC, Merritt A. Short- and long-term synaptic depression in rat neostriatum. J Neurophysiol. 1993; 70:1937–49. [PubMed: 7905031]
35. Wang Z, Kai L, Day M, Ronesi J, Yin HH, Ding J, et al. Dopaminergic control of corticostriatal long-term synaptic depression in medium spiny neurons is mediated by cholinergic interneurons. Neuron. 2006; 50:443–52. [PubMed: 16675398]
36. Gerdeman GL, Ronesi J, Lovinger DM. Postsynaptic endocannabinoid release is critical to long-term depression in the striatum. Nat Neurosci. 2002; 5:446–51. [PubMed: 11976704]
37. Mulkey RM, Endo S, Shenolikar S, Malenka RC. Involvement of a calcineurin/inhibitor-1 phosphatase cascade in hippocampal long-term depression. Nature. 1994; 369:486–88. [PubMed: 7515479]
38. Hansel C, de Jeu M, Belmeguenai A, Houtman SH, Buitendijk GH, Andreev D, et al. alphaCaMKII is essential for cerebellar LTD and motor learning. Neuron. 2006; 51:835–43. [PubMed: 16982427]
39. Partridge JG, Tang KC, Lovinger DM. Regional and postnatal heterogeneity of activity-dependent long-term changes in synaptic efficacy in the dorsal striatum. J Neurophysiol. 2000; 84:1422–29. [PubMed: 10980015]
40. Charpier S, Deniau JM. In vivo activity-dependent plasticity at corticostriatal connections: evidence for physiological long-term potentiation. Proc Natl Acad Sci USA. 1997; 94:7036–40. [PubMed: 9192687]
41. Norman ED, Egli RE, Colbran RJ, Winder DG. A potassium channel blocker induces a long-lasting enhancement of corticostriatal responses. Neuropharmacology. 2006; 48:311–21. [PubMed: 15695170]
42. Picconi B, Centonze D, Hakansson K, Bernardi G, Greengard P, Fisone G, et al. Loss of bidirectional striatal synaptic plasticity in L-DOPA-induced dyskinesia. Nat Neurosci. 2003; 6:501–6. [PubMed: 12665799]
43. Winder DG, Sweatt JD. Roles of serine/threonine phosphatases in hippocampal synaptic plasticity. Nat Rev Neurosci. 2001; 2:461–74. [PubMed: 11433371]
44. Gong S, Zheng C, Doughty ML, Losos K, Didkovsky N, Schambra UB, et al. A gene expression atlas of the central nervous system based on bacterial artificial chromosomes. Nature. 2003; 425:917–25. [PubMed: 14586460]
45. Heintz N. Gene expression nervous system atlas (GENSAT). Nat Neurosci. 2004; 7:483. [PubMed: 15114362]
46. Kreitzer AC, Malenka RC. Endocannabinoid-mediated rescue of striatal LTD and motor deficits in Parkinson's disease models. Nature. 2007; 445:643–7. [PubMed: 17287809]