Published in final edited form as:

Mov Disord. 2010 August 15; 25(11): 1568–1576. doi:10.1002/mds.23245.

Aberrant striatal plasticity is specifically associated with dyskinesia following L-DOPA treatment

Pauline Belujon, PhD^{*}, Daniel J. Lodge, PhD^{*,1}, and Anthony A. Grace, PhD

Departments of Neuroscience, Psychiatry, and Psychology, University of Pittsburgh, Pittsburgh, PA, USA

Abstract

Chronic L-DOPA treatment for Parkinson's disease often results in the development of abnormal involuntary movement, known as L-DOPA-induced dyskinesia (LIDs). Studies suggest that LIDs may be associated with aberrant cortico-striatal plasticity. Using in vivo extracellular recordings from identified type I and type II medium spiny striatal neurons, chronic L-DOPA treatment was found to produce abnormal cortico-striatal information processing. Specifically, following chronic L-DOPA treatment in dopamine-depleted rats, there was a transition from a cortically-evoked long-term depression (LTD) to a complementary but opposing form of plasticity, long-term potentiation, in type II 'indirect' pathway neurons. In contrast, LTD could still be induced in type I neurons. Interestingly, the one parameter that correlated best with dyskinesias was the inability to de-depress established LTD in type I medium spiny striatal neurons. Taken as a whole, we propose that the induction of LIDs is due, at least in part, to an aberrant induction of plasticity within the type II indirect pathway neurons combined with an inability to de-depress established plastic responses in type I neurons. Such information is critical for understanding the cellular mechanisms underlying one of the major caveats to L-DOPA therapy.

Keywords

Parkinson's disease; synaptic plasticity; dopamine; basal ganglia; motor cortex

Introduction

Parkinson's disease (PD) is characterized by a progressive degeneration of nigrostriatal dopaminergic neurons¹ and replacement therapy with the dopamine (DA) precursor L-3, 4-dihydroxyphenylalanine (L-DOPA) is the most effective therapy². Unfortunately, it often induces adverse fluctuations in motor response such as the end-of-dose "wearing off", and the development of involuntary movements, known as L-DOPA-induced dyskinesia (LID). Thus, patients may cycle between ON state complicated by LIDs and OFF state in which the motor symptoms re-emerge.

Several studies suggest that aberrant corticostriatal plasticity may underlie the development of LID^{3–5}. Recently, Picconi and colleagues have described plastic changes in the striatum of 6-hydroxydopamine (6-OHDA) lesioned rats displaying LID⁶, representing a significant

Correspondence should be addressed to Dr. Pauline Belujon, Departments of Neuroscience, Psychiatry, and Psychology, University of Pittsburgh, A210 Langley Hall, Pittsburgh, PA, 15260 USA. belujon@pitt.edu Tel. 412.624.7332 Fax. 412 624 9198.

^{*}These authors have contributed equally.

¹Current affiliation, Department of Pharmacology, UTHSCSA, 7703 Floyd Curl Drive, San Antonio, TX, 78229, USA.

Financial disclosure: Grants: Lundbeck; Boards: Puretech Ventures; Consultants: Johnson & Johnson, Taisho; Honoraria: Lilly

Author roles: Belujon: 1, 2, 3; Lodge: 1, 2, 3; Grace: 1, 2C, 3B

advance in understanding the mechanisms underlying this complication. One of the caveats of such studies is that the examination of neuroplasticity is performed in slices in which extracellular solutions are artificially modified to reduce extracellular Mg^{2+} , which would favor long-term potentiation (LTP) development^{6, 7}. This significantly alters the response consistently observed in the majority of studies examining neuroplasticity in the striatum using both in vitro and in vivo approaches^{8, 9}. Indeed, the prominent form of neuroplasticity observed in the striatum of rats upon application of high frequency stimulation is not LTP but rather a complimentary process known as long-term depression (LTD).

The striatum has two distinct output projection pathways¹⁰ and a significant literature suggests that the motor symptoms of PD arise due to an imbalance within these pathways^{11–13}. Thus, it is surprising that the majority of studies investigating synaptic plasticity in the striatum of PD and/or dyskinetic rats have failed to distinguish between these striatonigral and striatopallidal neurons.

Given evidence for altered synaptic plasticity associated with LID and evidence of alterations in direct vs indirect pathways in PD, we examined the regulation of striatal neuron plasticity in vivo in normal vs DA lesioned rats, and further subdividing L-DOPA-treated rats into those exhibiting dyskinesia and those that do not. We employed our previously established criteria¹⁴, further confirmed here, to distinguish striatonigral and striatopallidal neurons to determine whether synaptic plasticity is altered in the direct vs indirect pathways.

Methods

All experiments were performed in accordance with the guidelines outlined in the USPHS Guide for the Care and Use of Laboratory Animals and were approved by the Institutional Animal Care and Use Committee of the University of Pittsburgh.

6-OHDA Lesions and L-DOPA treatment

Unilateral 6-OHDA lesions of the medial forebrain bundle (mfb) were performed as previously described¹⁵. Following three weeks recovery, rats were treated twice daily with L-DOPA (10 mg/kg i.p.) and benserazide (7.5 mg/kg i.p.) or vehicle (saline 1 ml/kg i.p.) for three weeks. This dose of L-DOPA was specifically selected to induce dyskinesia in approximately 50% of the animals⁶.

AIMS Determination

The expression of L-DOPA-induced dyskinesia has been extensively studied^{6, 16, 17}. Thus, over the three-week period LIDs were examined using the standard abnormal involuntary movement (AIMs) scale and a test for limb asymmetry. Briefly, rats were placed individually in a glass cylinder 20 mins following the injection of L-DOPA/benserazide. AIMS were rated between 0–4 for orolingual, axial and limb over 5 mins. Limb asymmetry was determined by the number of wall contacts by the ipsilateral vs. contralateral forelimb over 5 mins.

Striatal Neuron Extracellular Recordings

Given that the effect of L-DOPA on striatal dopamine decreases after 6–7 hours^{18, 19}, rats were anesthetized with urethane (1.2g/kg i.p.) 12–24 hours following the last L-DOPA injection. Stimulation of the motor cortex (M1) and of the substantia nigra pars reticulata (SNr) was performed with bipolar concentric stimulating electrodes (NEX100). Extracellular glass microelectrodes (impedance 6–14MΩ) were lowered into the dorsal striatum and type I and II medium spiny neurons (MSN) were identified based on paired-

pulse (inter-stimulus interval: 100 ms) cortical stimulation as previously reported^{14, 20}. Antidromic activation of the SNr was used to further confirm the identity of striatonigral neurons. Once a stable putative MSN was identified, the stimulation intensity was adjusted to evoke an action potential approximately 50 % of the time and the baseline response to M1 stimulation (0.5 Hz pulses) was recorded for 20 mins. After the baseline period, high frequency stimulation (HFS) of the M1 pathway (3 × 2 s trains, 1 mA, 50 Hz, at a rate of 0.05 trains per second) was applied. The response to M1 stimulation was recorded for a further 40 mins before low frequency stimulation (LFS) of the M1 pathway (5 Hz, 500 pulses, 1 mA). M1 evoked responses were examined for an additional 40 mins.

Combined Retrograde Tracing and Juxtacellular Recordings

For retrograde tracing experiments both control and unilateral 6-OHDA lesioned rats (250–300g) were anesthetized with ketamine/xylazine (80/12mg/kg i.p. respectively). Recombinant cholera toxin subunit B conjugated to Alexa Fluor 488 (1.0 µg in 0.5 µl dPBS) was microinjected into the external globus pallidus. Following one week recovery, rats were anaesthetized with urethane (1.2g/kg i.p.) and type I and II MSN's were identified by paired-pulse M1 stimulation. Extracellular glass microelectrodes (in situ impedance 40–80MΩ) filled with 2% Neurobiotin were connected to an Axoclamp-2A amplifier in bridge mode to enable simultaneous recording and current injection. Once a stable putative MSN was identified, current (+1 to +4 nA, 200 ms duration, 2 Hz) was passed and the cell entrained to depolarizing current steps.

Histology

At the cessation of experiments, the recording site was marked via electrophoretic ejection of Pontamine sky blue dye (–25 µA constant current: 20–30 mins) and iron deposited by passing constant current (0.3 mA, 10 s) across the stimulating electrode. Rats were perfused transcardially with paraformaldehyde, decapitated, and their brains removed and post-fixed for 24 hours. Brains were cryoprotected then sliced coronally (60 µm). Sections were Nissl stained for histochemical verification with reference to a stereotaxic atlas²¹. Additional sections of striatum were processed for tyrosine hydroxylase immunoreactivity as previously described²² (Supplemental Fig S1). Juxtacellularly labelled cells were processed with streptavidin-Alexa Fluor 594.

Analysis

Electrophysiological analysis was performed using custom-designed software (Neuroscope). Densitometric analysis of each striatal section was performed with reference to the M1 contralateral to the lesion using the SCION imaging system (PC version of NIH image). All data are represented as the mean ± the standard error of the mean (S.E.M.). Data were analyzed using a one-way ANOVA with repeated measures followed by the Holm-Sidak test. Multiple comparisons were analyzed using a two-way ANOVA followed by the Holm-Sidak test (SigmaStat software program, Systat Software Inc).

Detailed methodology is described in the Supplementary Methods.

Results

All 6-OHDA-lesioned rats used in this study demonstrated a substantial loss of striatal tyrosine-hydroxylase immunoreactivity in comparison with intact animals (–93.3 ± 0.9 % decrease, n=62).

Behavior

As previously described, repeated L-DOPA induced gradual development of dyskinesia in approximately 50 % of 6-OHDA-lesioned rats^{6, 16, 17}. A significant increase in AIMS was observed for one group of rats (dyskinetic) after day 6 and increased gradually until day 17 (day 1: 0.26 ± 0.13 axial AIMS; 0.44 ± 0.17 limb AIMS; 0.07 ± 0.07 orolingual AIMS; day 17: 3.52 ± 0.23 axial AIMS; 3.74 ± 0.16 limb AIMS; 3.62 ± 0.22 orolingual AIMS; $p < 0.05$; $n = 27$) (Fig 1 A to C). A gradual increase in the limb-use asymmetry score was also observed (day 1: -5.7 ± 10.6 %; day 17: 64.8 ± 10.2 %, $p < 0.05$, $n = 27$) (Fig 1D). The non-dyskinetic group failed to show significant changes in AIMS (day 1: 0.08 ± 0.05 axial AIMS; 0.17 ± 0.12 limb AIMS; no orolingual AIMS; day 17: no axial AIMS; 0.29 ± 0.16 limb AIMS; 0.04 ± 0.04 orolingual AIMS; NS; $n = 24$; Fig 1 A to C) or limb-use asymmetry score (day 1: -26.8 ± 10.3 %; day 17: -28.3 ± 7.6 %, NS, $n = 24$; Fig 1D). Thus, consistent with previous characterizations, the expression of LIDs was extremely robust with rats displaying either a full complement of axial, orofacial and limb AIMS or no dyskinesias.

Identification of striatal neurons

Striatonigral (type I) and striatopallidal (type II) neurons were distinguished by their response to cortical stimulation, as described previously¹⁴ (Fig 2 and 3). Thus, striatonigral neurons responded to the paired cortical stimulation with a higher probability of spike generation in response to the first pulse, whereas striatopallidal neurons were more responsive to the second pulse (Fig 2 and 3)¹⁴. The identification of these distinct MSNs was confirmed by antidromic activation from the SNr as well as juxtacellular labeling combined with retrograde tracing from the GP. Specifically, identified type I neurons were consistently antidromically activated from the SNr whereas type II neurons were not (Fig 2; type I: 12/19 neurons; type II: 5/25; $p < 0.05$, $z = 2.60$, z-test with Yates correction). Furthermore, juxtacellularly-labeled type II neurons were consistently labeled retrogradely from the GP, whereas type I neurons were devoid of retrograde tracer (Fig 3; type I: 2/14 neurons; type II: 8/12; $p < 0.05$, $z = 2.33$ z-test with Yates correction). These data substantiate our previous characterizations of type I and type II neurons as MSNs comprising the direct and indirect pathways, respectively^{14, 20, 23}.

Synaptic plasticity in intact and lesioned animals

Consistent with previous results^{24, 25}, HFS of the corticostriatal pathway of intact rats induced LTD of cortically-evoked action potential generation in both types of neurons (striatonigral: $p < 0.05$, $n = 8/8$; striatopallidal: $p < 0.05$, $n = 6/8$; Fig 4A and B). In lesioned rats, the majority of striatopallidal neurons didn't exhibit LTD following HFS (ns; $n = 8/10$; Fig 4D), confirming the block of corticostriatal plasticity after dopaminergic denervation^{6, 26}. Interestingly, striatonigral neurons in lesioned animals still exhibited LTD after HFS ($p < 0.05$; $n = 7/7$) that was not significantly different from the response recorded in intact animals (ns; Fig 4C). All average values are summarized in supplemental table 1.

LFS consistently reverses established plasticity in corticostriatal synapses^{4, 6, 9, 27, 28}. Thus, LFS performed 40 minutes after HFS induced no change in striatopallidal neurons of intact and lesioned animals (ns; $n = 8$ and $n = 7$, respectively, Fig 4B and D). Comparison of evoked activity following HFS with that post LFS revealed a significant reversal of the LTD in striatonigral neurons of control animals ($p < 0.05$; $n = 8$, Fig 4A). Moreover, this return to baseline is lost after 6-OHDA lesions ($p < 0.05$ in comparison with control; $n = 7$) (Fig 4C).

Synaptic plasticity in L-DOPA treated non-dyskinetic and dyskinetic rats

LTD and LTP are long-term changes in synaptic efficacy that constitute one of the cellular models for information storage. In addition, depotentiation and de-depression represent another level of plasticity and can alter past synaptic information processing²⁹. Previous studies have suggested that aberrant depotentiation may lead to the development of abnormal motor patterns⁶. Therefore, we assessed synaptic plasticity changes in both L-DOPA treated dyskinetic and non-dyskinetic rats. In striatonigral neurons, LTD was induced by cortical HFS in both non-dyskinetic ($p < 0.05$; $n = 5/7$; Fig 5A) and dyskinetic rats ($p < 0.05$; $n = 7/9$; Fig 5C). No significant differences were observed between the LTD in dyskinetic and non-dyskinetic rats (ns; Fig 5A, $n = 7$ and Fig 5C, $n = 5$, respectively). In non-dyskinetic rats, LFS attenuated the HFS-evoked LTD ($-22.4 \pm 9.9\%$; $p < 0.05$; $n = 5$), whereas no effect on the LTD in dyskinetic rats was observed (ns; $n = 5$).

Interestingly, HFS in striatopallidal neurons induced changes in synaptic plasticity in both dyskinetic and non-dyskinetic rats. Thus, in contrast to the LTD observed in untreated rats in vivo, HFS induced a complementary but opposite form of synaptic plasticity, i.e. LTP. As a result, an increase in the cortical-evoked spike probability of MSNs was observed following HFS in both non-dyskinetic ($p < 0.05$; $n = 9/11$; Fig 5B) and dyskinetic rats ($p < 0.05$; $n = 9/12$; Fig 5D). Moreover, LFS fully reversed the LTP in type II neurons from dyskinetic rats ($p < 0.05$ in comparison with 20 minutes after HFS and ns in comparison with control; $n = 6$), whereas non-dyskinetic rats failed to show reversal by LFS (ns compared to 20 minutes after HFS, $p < 0.05$ compared to control; $n = 9$).

Discussion

The data presented here demonstrate major adaptive changes in corticostriatal information processing following chronic L-DOPA administration in the hemi-parkinsonian rat model. Specifically, we report that the primary deficit in synaptic information processing observed following 6-OHDA lesion is the inability to induce corticostriatal LTD in indirect pathway neurons. In addition we demonstrate that chronic L-DOPA treatment results in dramatic alterations in both the induction and normalization of synaptic plasticity in both direct and indirect pathway MSNs.

Based on intracellular staining and responses to dopamine agonists the characterization of type I and type II neurons and their identification as neurons corresponding to the 'direct' and 'indirect' pathways, respectively, has been extensively documented²³. In the present study, this characterization has been confirmed using retrograde tracing (from the GP) combined with juxtacellular labeling as well as by antidromic activation from the SNr. It should be noted that antidromic activation of striatal neurons has been considered unreliable¹⁴, presumably due to current shunting by K^+ channels^{14, 30}. Indeed, in the present study, 35% of type I neurons failed to show an antidromic response. This could be the reason why a recent set of publications report the opposite characterization of MSN's based exclusively on antidromic activation from the SNr³¹.

HFS of the motor cortex has been demonstrated consistently to induce LTD of cortically-evoked action potentials in striatal MSNs in vitro⁹ as well as in vivo^{8, 32}. In the current study, changes in plasticity, either potentiation or depression, were measured as changes in spike probability. HFS resulted in the induction of LTD in both striatonigral and striatopallidal neurons of control rats. Following 6-OHDA lesion, LTD could still be evoked in striatonigral neurons; in contrast, there was no significant effect of cortical HFS in striatopallidal neurons. These data are consistent with previous studies examining the role of dopamine D1 and D2 receptors in corticostriatal plasticity. Thus, corticostriatal LTD can be

attenuated by sulpiride, and is absent in brain slices from both 6-OHDA lesioned rats⁷ and mice lacking D2 receptors³³. Thus, the absence of LTD in striatopallidal neurons observed in the current study is consistent with previous data reporting the dependence of LTD on D2 receptor activation³⁴. In contrast to the effect on striatopallidal neurons, there was no effect of unilateral DA depletion on the ability of cortical HFS to induce LTD in striatonigral neurons. This result is consistent with previous studies showing that corticostriatal LTD persists in mice lacking D1 receptors²⁷, although D1 receptors antagonists will block corticostriatal LTD³⁵. Taken together, our data suggest that a decrease in DA levels within the striatum would result in the loss of a component essential for the development of LTD predominantly in striatopallidal neurons, and a loss of control over motor inhibition.

Although corticostriatal plasticity following chronic treatment with L-DOPA has been investigated previously, such studies were limited in their interpretation due to several important factors: 1) these studies were performed in vitro in which afferent processes have been severed⁶; 2) changes in LTP were biased by either depolarization of the neuronal membrane in vivo³⁶ or omission of magnesium ions in vitro^{6, 7}; and 3) neurons of the direct and indirect pathway were not distinguished, confounding the interpretation of the functional outcome of the observed changes. Thus, we examined the effect of chronic L-DOPA treatment on corticostriatal plasticity in both striatonigral and striatopallidal neurons. Consistent with our observation that unilateral DA depletion only altered activity-dependent plasticity in striatopallidal neurons, the alterations in HFS-induced corticostriatal plasticity observed following chronic L-DOPA administration were restricted to the indirect projection neurons. Indeed, there was no disruption in cortically-evoked LTD in direct projecting neurons following DA denervation or after chronic L-DOPA treatment, suggesting that the induction of corticostriatal plasticity in striatopallidal neurons is not sensitive to tonic changes in dopaminergic transmission. In contrast, our most striking result is that chronic L-DOPA treatment resulted in a transition from cortically-evoked LTD to the complementary but opposite process of LTP in striatopallidal neurons. This is consistent with previous studies showing that HFS of cortical fibers from D2 receptor mutant mice robustly induces an NMDA independent LTP²⁷. Such a significant change in corticostriatal information processing is likely to have a dramatic effect on motor output under conditions of high cortical activity, and interfere with the ability of the indirect pathway to effectively modulate direct pathway motor output.

Previous data suggested that aberrant de-potentialization of LTP may play a role in LIDs. Thus, low frequency stimulation of cortical afferents can reverse LTP evoked by HFS⁶. Similarly, in the present study LFS was able to attenuate LTD evoked by cortical HFS in striatonigral neurons recorded from intact rats. In contrast in hemiparkinsonian rats, LFS further depressed cortically driven responses suggesting a potential dopamine-dependent mechanism contributing to de-depression.

Interestingly, whereas no differences in HFS-evoked responses were observed between dyskinetic and non-dyskinetic rats, significantly different results were seen following LFS. Thus, chronic L-DOPA appeared to repair the deficit in LTD reversal observed in striatonigral neurons of lesioned rats, but only in the non-dyskinetic rats. In contrast, the deficit in LTD-reversal was retained in striatonigral neurons of dyskinetic rats. These data are in agreement, at least in part, with previous experiments reporting that rats displaying LIDs fail to reverse HFS-induced LTP in unidentified striatal neurons recorded in vitro⁶. Our data suggest a loss of regulation over LTD in dyskinetic rats causing the striatonigral neurons to retain abnormally large depression of responses. Such an imbalance may be further exacerbated by the indirect neurons, which were found to display LTP (rather than LTD) following chronic L-DOPA treatment; an effect that could be reversed by LFS only in dyskinetic rats but not in non-dyskinetic rats. Consequently, in dyskinetic rats the regulation

of synaptic plasticity in direct and indirect pathways are out of balance; LTD in striatonigral neurons is abnormally persistent and fails to be down-modulated, whereas in striatopallidal neurons LTP is abnormally sensitive to reversal. As such, there would be a strong attenuation in the ability of the indirect pathway to regulate the direct pathway during low activity periods.

One potential caveat in the interpretation of the current results is that chronic L-DOPA treatment exhibited substantial effects in both dyskinetic and non-dyskinetic rats. However, it must be noted that all rats in the current study were recorded in the drug-free state while the expression of LIDs is most prominent during peak cerebrospinal fluid levels of L-DOPA³⁷. Nonetheless, it has been suggested that the potential clinical actions of chronic L-DOPA administration arise from the induction of a priming effect that only manifests as LID during high levels of the drug³⁸. Thus, we propose that the aberrant corticostriatal plasticity in indirect pathway neurons may be responsible, at least in part, for the so called “priming” of the system. In addition, a deficit in the ability to reverse established plastic changes in direct neurons is observed only in L-DOPA-treated rats that display dyskinesia in response to an acute L-DOPA injection. This inability to reverse established plasticity is suggested to result in a pathological storage of nonessential motor information. Thus the aberrant induction of striatal plasticity in striatopallidal neurons combined with the disparate response to LFS in striatonigral and striatopallidal neurons during OFF states could facilitate LIDs expression during ON states.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors thank Niki MacMurdo & Emily Mahar for their technical assistance, Brian Lowry for the production, development and support with the custom designed electrophysiology software (Neuroscope) and Kathryn Gill for critical reading and helpful discussions. This work was supported by the USPHS DA15408 and MH57440 (AAG), a Young Investigator Award from NARSAD - The Mental Health Research Association (DJL) and an award from Fondation pour la Recherche Medicale (PB).

This work was supported by the USPHS DA15408 and MH57440 (AAG), a Young Investigator Award from NARSAD - The Mental Health Research Association (DJL) and an award from Fondation pour la Recherche Medicale (PB).

References

1. Ehringer H, Hornykiewicz O. Distribution of noradrenaline and dopamine (3-hydroxytyramine) in the human brain and their behavior in diseases of the extrapyramidal system. *Klin Wochenschr.* 1960; 38:1236–1239. [PubMed: 13726012]
2. Marsden CD, Parkes JD. Success and problems of long-term levodopa therapy in Parkinson's disease. *Lancet.* 1977; 1(8007):345–349. [PubMed: 64868]
3. Bedard PJ, Blanchet PJ, Levesque D, et al. Pathophysiology of L-dopa-induced dyskinesias. *Mov Disord.* 1999; 14(Suppl 1):4–8. [PubMed: 10493397]
4. Calabresi P, Giacomini P, Centonze D, Bernardi G. Levodopa-induced dyskinesia: a pathological form of striatal synaptic plasticity? *Ann Neurol.* 2000; 47(4 Suppl 1):S60–68. discussion S68-69. [PubMed: 10762133]
5. Chase TN, Oh JD. Striatal dopamine- and glutamate-mediated dysregulation in experimental parkinsonism. *Trends Neurosci.* 2000; 23(10 Suppl):S86–91. [PubMed: 11052225]
6. Picconi B, Centonze D, Hakansson K, et al. Loss of bidirectional striatal synaptic plasticity in L-DOPA-induced dyskinesia. *Nat Neurosci.* 2003; 6(5):501–506. [PubMed: 12665799]

7. Calabresi P, Pisani A, Mercuri NB, Bernardi G. Long-term Potentiation in the Striatum is Unmasked by Removing the Voltage-dependent Magnesium Block of NMDA Receptor Channels. *Eur J Neurosci.* 1992; 4(10):929–935. [PubMed: 12106428]
8. Mahon S, Deniau JM, Charpier S. Corticostriatal plasticity: life after the depression. *Trends Neurosci.* 2004; 27(8):460–467. [PubMed: 15271493]
9. Pisani A, Centonze D, Bernardi G, Calabresi P. Striatal synaptic plasticity: implications for motor learning and Parkinson's disease. *Mov Disord.* 2005; 20(4):395–402. [PubMed: 15719415]
10. Le Moine C, Bloch B. D1 and D2 dopamine receptor gene expression in the rat striatum: sensitive cRNA probes demonstrate prominent segregation of D1 and D2 mRNAs in distinct neuronal populations of the dorsal and ventral striatum. *J Comp Neurol.* 1995; 355(3):418–426. [PubMed: 7636023]
11. Gerfen CR. Molecular effects of dopamine on striatal-projection pathways. *Trends Neurosci.* 2000; 23(10 Suppl):S64–70. [PubMed: 11052222]
12. Obeso JA, Rodriguez-Oroz MC, Rodriguez M, et al. Pathophysiology of the basal ganglia in Parkinson's disease. *Trends Neurosci.* 2000; 23(10 Suppl):S8–19. [PubMed: 11052215]
13. Onn SP, West AR, Grace AA. Dopamine-mediated regulation of striatal neuronal and network interactions. *Trends Neurosci.* 2000; 23(10 Suppl):S48–56. [PubMed: 11052220]
14. Onn SP, Berger TW, Grace AA. Identification and characterization of striatal cell subtypes using in vivo intracellular recording in rats: I. Basic physiology and response to corticostriatal fiber stimulation. *Synapse.* 1994; 16(3):161–180. New York, NY. [PubMed: 8197579]
15. Belujon P, Bezard E, Taupignon A, Bioulac B, Benazzouz A. Noradrenergic modulation of subthalamic nucleus activity: behavioral and electrophysiological evidence in intact and 6-hydroxydopamine-lesioned rats. *J Neurosci.* 2007; 27(36):9595–9606. [PubMed: 17804620]
16. Lundblad M, Andersson M, Winkler C, Kirik D, Wierup N, Cenci MA. Pharmacological validation of behavioural measures of akinesia and dyskinesia in a rat model of Parkinson's disease. *Eur J Neurosci.* 2002; 15(1):120–132. [PubMed: 11860512]
17. Cenci MA, Lee CS, Bjorklund A. L-DOPA-induced dyskinesia in the rat is associated with striatal overexpression of prodynorphin- and glutamic acid decarboxylase mRNA. *Eur J Neurosci.* 1998; 10(8):2694–2706. [PubMed: 9767399]
18. Napolitano A, Zurcher G, Da Prada M. Effects of tolcapone, a novel catechol-O-methyltransferase inhibitor, on striatal metabolism of L-dopa and dopamine in rats. *European journal of pharmacology.* 1995; 273(3):215–221. [PubMed: 7737328]
19. Rodriguez M, Morales I, Gonzalez-Mora JL, et al. Different levodopa actions on the extracellular dopamine pools in the rat striatum. *Synapse.* 2007; 61(2):61–71. New York, NY. [PubMed: 17117421]
20. Onn SP, Berger TW, Grace AA. Identification and characterization of striatal cell subtypes using in vivo intracellular recording in rats: II. Membrane factors underlying paired-pulse response profiles. *Synapse.* 1994; 16(3):195–210. New York, NY. [PubMed: 8197582]
21. Paxinos, G.; Watson, C. *The Rat Brain in Stereotatic Coordinates.* Academic Press; San Diego: 1996.
22. Jedema HP, Grace AA. Chronic exposure to cold stress alters electrophysiological properties of locus coeruleus neurons recorded in vitro. *Neuropsychopharmacology.* 2003; 28(1):63–72. [PubMed: 12496941]
23. Onn SP, Berger TW, Grace AA. Identification and characterization of striatal cell subtypes using in vivo intracellular recording and dye-labeling in rats: III. Morphological correlates and compartmental localization. *Synapse.* 1994; 16(3):231–254. New York, NY. [PubMed: 8197584]
24. Lovinger DM, Tyler EC, Merritt A. Short- and long-term synaptic depression in rat neostriatum. *J Neurophysiol.* 1993; 70(5):1937–1949. [PubMed: 7905031]
25. Ronesi J, Lovinger DM. Induction of striatal long-term synaptic depression by moderate frequency activation of cortical afferents in rat. *J Physiol.* 2005; 562(Pt 1):245–256. [PubMed: 15498813]
26. Centonze D, Calabresi P, Giacomini P, Bernardi G. Neurophysiology of Parkinson's disease: from basic research to clinical correlates. *Clin Neurophysiol.* 1999; 110(12):2006–2013. [PubMed: 10616104]

27. Centonze D, Grande C, Saulle E, et al. Distinct roles of D1 and D5 dopamine receptors in motor activity and striatal synaptic plasticity. *J Neurosci*. 2003; 23(24):8506–8512. [PubMed: 13679419]
28. Dalbem A, Silveira CV, Pedroso MF, et al. Altered distribution of striatal activity-dependent synaptic plasticity in the 3-nitropropionic acid model of Huntington's disease. *Brain research*. 2005; 1047(2):148–158. [PubMed: 15901483]
29. Yasui T, Fujisawa S, Tsukamoto M, Matsuki N, Ikegaya Y. Dynamic synapses as archives of synaptic history: state-dependent redistribution of synaptic efficacy in the rat hippocampal CA1. *J Physiol*. 2005; 566(Pt 1):143–160. [PubMed: 15845579]
30. Fitzpatrick JS, Akopian G, Walsh JP. Short-Term Plasticity at Inhibitory Synapses in Rat Striatum and Its Effects on Striatal Output. *J Neurophysiol*. 2001; 85(5):2088–2099. [PubMed: 11353025]
31. Mallet N, Ballion B, Le Moine C, Gonon F. Cortical inputs and GABA interneurons imbalance projection neurons in the striatum of parkinsonian rats. *J Neurosci*. 2006; 26(14):3875–3884. [PubMed: 16597742]
32. Reynolds JN, Wickens JR. Substantia nigra dopamine regulates synaptic plasticity and membrane potential fluctuations in the rat neostriatum, in vivo. *Neuroscience*. 2000; 99(2):199–203. [PubMed: 10938425]
33. Calabresi P, Saiardi A, Pisani A, et al. Abnormal synaptic plasticity in the striatum of mice lacking dopamine D2 receptors. *J Neurosci*. 1997; 17(12):4536–4544. [PubMed: 9169514]
34. Wang Z, Kai L, Day M, et al. Dopaminergic control of corticostriatal long-term synaptic depression in medium spiny neurons is mediated by cholinergic interneurons. *Neuron*. 2006; 50(3):443–452. [PubMed: 16675398]
35. Calabresi P, Maj R, Pisani A, Mercuri NB, Bernardi G. Long-term synaptic depression in the striatum: physiological and pharmacological characterization. *J Neurosci*. 1992; 12(11):4224–4233. [PubMed: 1359031]
36. Charpier S, Deniau JM. In vivo activity-dependent plasticity at cortico-striatal connections: evidence for physiological long-term potentiation. *Proc Natl Acad Sci U S A*. 1997; 94(13):7036–7040. [PubMed: 9192687]
37. Olanow CW, Gauger LL, Cedarbaum JM. Temporal relationships between plasma and cerebrospinal fluid pharmacokinetics of levodopa and clinical effect in Parkinson's disease. *Annals of Neurology*. 1991; 29(5):556–559. [PubMed: 1859185]
38. Blanchet PJ, Calon F, Morissette M, et al. Relevance of the MPTP primate model in the study of dyskinesia priming mechanisms. *Parkinsonism Relat Disord*. 2004; 10(5):297–304. [PubMed: 15196509]

Figure 1.

Behavioral testing for the expression of L-DOPA induced dyskinesia. Dyskinetic rats demonstrated an increase in axial (A), limb (B) and orolingual (C) AIMS over treatment days and a contralateral limb asymmetry bias compared to non-dyskinetic rats (D). * represents significant difference between dyskinetic and non-dyskinetic rats ($p < 0.05$; 2-way ANOVA: Holm-Sidak post-hoc; $n = 24-27$ rats/group).

Figure 2.

Characterization of striatonigral and striatopallidal neurons by antidromic activation from substantia nigra pars reticulata. A representative example of the response to paired pulse stimulation in a SNr-projecting, type I (A) and non-SNr projecting, type II neuron (D). Twenty overlaid consecutive traces are shown with the numbers in brackets demonstrating the number of evoked spikes for the first and second cortical stimuli (A and D). The spike probability for the type I neuron was 0.65 for the first stimulation and 0.25 for the second (A) whereas the spike probability of the type II neurons was 0.25 for the first and 0.9 for the second stimulation. Electrical activation of the SNr induces a reliable antidromic action potential in type I (but not type II) neurons (B and E). Furthermore the action potential induced by SNr stimulation was confirmed to be antidromic by collision with a cortical evoked spike (C).

Figure 3. Characterization of type I and II medium spiny neurons by juxtacellular labeling and retrograde labeling from the external globus pallidus. Representative photomicrographs of juxtacellularly labeled neurons (red) and GP retrogradely labeled neurons (green) throughout the CPU. Type I neurons identified by paired pulse cortical stimulation (D) do not reliably innervate the GP (A–C). In contrast, type II neurons primarily comprise the indirect, striato-pallidal neurons (F–H). E and F demonstrate reliable entrainment of the medium spiny neuron to the depolarizing current pulses.

Figure 4.

6-OHDA lesions block the HFS-evoked LTD in striatopallidal but not in striatonigral neurons. HFS (open circles) induces a decrease of the cortical-evoked activity in both striatonigral (A) and striatopallidal (B) neurons in intact animals (left panels). LFS (open squares) produces a return to the baseline in striatonigral but not in striatopallidal neurons of intact rats (left panels). 6-OHDA lesions (right panels) prevent HFS-evoked LTD in striatopallidal neurons, while the response in striatonigral neurons remains intact. LFS further augments the LTD induced by HFS in striatonigral neurons, but has no significant effect on type II neurons. Inserts represent the average spike probability (mean $\pm$ SEM) in baseline (black), after HFS (dark grey) and after LFS (light grey). * represents significant difference between groups ($p < 0.05$; 1-way ANOVA: Holm-Sidak post-hoc: $n = 6-8$ neurons/group).

Figure 5.

Chronic L-DOPA treatment enables HFS-evoked LTP in both dyskinetic and non-dyskinetic rats in striatopallidal neurons, but its reversal with LFS is selectively altered in dyskinetic rats. Striatonigral neurons (top panels) exhibit LTD after HFS in both non-dyskinetic (left) and dyskinetic (right) rats (open circles). In contrast, striatopallidal neurons (bottom) display a significant LTP in both dyskinetic (left) and non dyskinetic (right) rats after HFS (open circles). A reversal of LTD induced by LFS is observed in striatopallidal neurons only in the dyskinetic rats. These data suggest that the LTP is more labile in dyskinetic rats following chronic L-DOPA treatment. Inserts represent the average spike probability (mean $\pm$ SEM) in baseline (black), after HFS (dark grey) and after LFS (light grey). * represents significant difference between groups ($p < 0.05$; 1-way ANOVA: Holm-Sidak post-hoc: $n = 6-8$ neurons/group).