Therapeutic doses of L-dopa reverse hypersensitivity of corticostriatal D2-dopamine receptors and glutamatergic overactivity in experimental parkinsonism

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Summary
Levodopa (L-dopa) therapy is still considered the gold-standard in the treatment of Parkinson’s disease. However, the synaptic and cellular mechanisms involved in the amelioration of motor symptoms during this treatment are still unclear. To address this issue, we analysed the physiological and pharmacological properties of striatal glutamatergic and GABAergic synaptic transmission in an experimental model of Parkinson’s disease. Single-cell recordings were performed in sham-operated rats, in 6-hydroxydopamine-lesioned animals and in rats receiving chronic L-dopa treatment following dopamine (DA) denervation. We utilized a dose of L-dopa (10 mg/kg, twice daily for 21 days) able to reverse motor deficits in about half of parkinsonian animals. In the striatum of parkinsonian animals showing therapeutic benefits following L-dopa treatment, we observed a reversal of glutamatergic overactivity and of the hypersensitivity of presynaptic D2 DA receptors controlling glutamate release from corticostriatal terminals. Conversely, no change was detected in the sensitivity of presynaptic D2 DA receptors modulating striatal GABA transmission in both parkinsonian and L-dopa-treated rats. We suggest that the reversal of striatal glutamatergic overactivity and the normalization of hypersensitive D2 DA receptors modulating excitatory transmission might underlie some of the therapeutic actions of L-dopa in Parkinson’s disease.

Keywords: basal ganglia; dopamine; excitatory synaptic transmission; Parkinson’s disease

Abbreviations: CNQX = 6-cyano-7-nitroquinoxaline-2,3-dione; DA = dopamine; DAergic = dopaminergic; EC50 = concentration of inhibitor at 50% maximal inhibition; EPSC = excitatory postsynaptic current; eEPSC = evoked excitatory postsynaptic currents; IPSC = inhibitory postsynaptic current; t-dopa = 3,4-dihydroxyphenyl-alanine methyl ester; MK-801 = (+)-MK-801 maleate; 6-OHDA = 6-hydroxydopamine; sEPSC = spontaneous excitatory postsynaptic currents; SN = substantia nigra


Introduction
Parkinson’s disease symptoms originate from the degeneration of the neural connection between the substantia nigra (SN) and the striatum, two brain nuclei essential for normal motor function (Graybiel, 2000; Graybiel et al., 2000). The striatum receives its dopaminergic (DAergic) inputs from neurons of SN (Smith and Bolam, 1990). Striatal dopamine (DA) deficiency, and the resultant changes in motor circuitry, is believed to underlie many of the clinical manifestations of Parkinson’s disease (Albin et al., 1989; Crossman, 1989; Greenamyre, 1993). The loss of the DA-mediated control of striatal neuronal activity is therefore generally considered as the functional substrate of the motor symptoms of Parkinson’s disease.

The striatum is also considered to be the main site of action of the substitutive pharmacological agent levodopa (L-dopa), the action of which is directed towards a restoration of
physiological concentrations of DA in this brain area (Papa et al., 1995; Calabresi et al., 2000; Chase and Oh, 2000; Picconi et al., 2002).

The lesion of the ascending nigrostriatal DA pathway by 6-hydroxydopamine (6-OHDA) injection in the unilateral SN mimics some aspects of parkinsonian pathology (Ungerstedt, 1968; Schwarting and Huston, 1996). Moreover, complex morphological changes, such as an altered density of asymmetric contacts on dendritic spines and an abnormal number of perforated synapses, have been reported in striatal neurons of parkinsonian animals (Ingham et al., 1998) as well as in the brain of Parkinson’s disease patients (Anglade et al., 1996). These morphological changes may lead to functional alterations of striatal glutamatergic transmission. Accordingly, an increased glutamatergic transmission in the striatum has been reported following DA denervation (Lindefors and Ungerstedt, 1990; Calabresi et al., 1993; Tang et al., 2001). Moreover, upregulation of D2-like receptors might also deeply alter excitatory and inhibitory synaptic transmission in experimental parkinsonism and in Parkinson’s disease patients. In line with this hypothesis, we found that DA-denervation reveals a presynaptic inhibitory effect mediated by D2-like receptors on glutamatergic inputs (Calabresi et al., 1993).

Whether chronic L-dopa treatment corrects these striatal abnormalities induced by DA denervation is still unknown. We have recently reported that in some parkinsonian animals, chronic treatment with therapeutic doses of L-dopa corrected behavioural abnormalities and restored bidirectional synaptic plasticity in the striatum (Picconi et al., 2003). Taking the advantage of this experimental model of Parkinson’s disease, in the present study we further investigated the synaptic mechanisms underlying the therapeutic effects of L-dopa in the group of animals showing motor improvement following the treatment. In particular, we analysed whether L-dopa reverses the glutamatergic overactivity and the hypersensitivity of presynaptic D2-like receptor induced by DA denervation. The results obtained may help to understand the molecular and synaptic target of DA-mediated restorative therapy in Parkinson’s disease.

Material and methods
All the experiments were approved by the Institutional Animal Care and Use Committee and performed according to The Guidelines of The European Union Council.

Nigrostriatal lesion and L-dopa treatment
To obtain unilateral nigrostriatal lesions, adult male Wistar rats (150–250 g, n = 60) [anaesthetized with 400 mg/kg of chloral hydrate intraperitoneally (i.p.)] were injected with 6-OHDA (8 μg/μl of saline containing 0.1% ascorbic acid) via a Hamilton syringe into the SN, at a rate of 0.38 μl/min, under stereotaxic coordinates (Paxinos and Watson, 1986). Sham-operated rats were injected with vehicle at the same coordinates. Fifteen days later, the rats were tested with 0.05 mg/kg subcutaneous injection of apomorphine, and the contralateral turns were counted with automatic rotometers for 1 h. Only those rats consistently making at least 400 contralateral turns were used for the electrophysiological recordings performed ~45 days later (2 months after the lesion), to avoid possible interference of apomorphine treatment with the plastic changes occurring in D2 receptor function following chronic DAergic denervation.

Some of these 6-OHDA-lesioned rats were anaesthetized with diethyl ether 10–40 days after apomorphine treatment, and brain dissection confirmed that the nigrostriatal pathway was lesioned. This was established by the observation of a >95% loss of DA neurons in the SN and the almost complete absence of DA terminals in the striatum. This was monitored using a monoclonal antibody for tyrosine–hydroxylase (Sigma–Aldrich, Milan, Italy) (Picconi et al., 2002, 2003).

A group of 6-OHDA-lesioned rats received L-dopa (10 mg/kg) plus benserazide (6.5 mg/kg) twice daily i.p. for 3 weeks. Benserazide was given to prevent decarboxylation of L-dopa in the periphery, as commonly used in clinical practice.

Behavioural tests
The limb-use asymmetry test (Schallert et al., 2000; Picconi et al., 2003) was performed on one occasion prior to 6-OHDA lesion surgery and twice a week during the L-dopa treatment period. Each rat was introduced into a transparent cylinder individually and monitored by a specific software system for 5 min, i.e. from 20 to 25 min after the injection of L-dopa. The number of supporting wall contacts executed independently with the right or the left forelimb was counted. The percentage of wall contacts executed by the impaired forelimb (contralateral to the lesion) was then subtracted from the percentage of contacts of the non-impaired forelimb to obtain a limb-use asymmetry score. A RotaRod System constant and accelerating treadmills (TSE Technical & Scientific Equipment GmbH, Bad Homburg, Germany) was used to study coordinated locomotor activity. All animals were trained during at least one session before the 6-OHDA lesion, and tested after the lesion, both before and at the end of the L-dopa treatment period (treatment days 13–21; testing interval, from 20 to 50 min post-L-dopa injection). The rats were placed on the rod and sequentially tested at 4, 12, 20, 28, 36 and 40 rotations per minute (r.p.m.) for a maximum of 300 s at each speed. Overall rod performance was expressed as the integral of time spent on the rod versus turning speeds (Rozas et al., 1997; Picconi et al., 2003).

Electrophysiology
Two months after saline or 6-OHDA injection into the SN, sham-operated, 6-OHDA-treated and 6-OHDA plus L-dopa-treated rats were used for all the experiments. The preparation and maintenance of coronal corticostriatal slices have been described previously (Calabresi et al., 1990, 1994). Briefly, corticostriatal slices (200–300 μm) were prepared from tissue blocks of the brain with the use of a vibratome. A single slice was transferred to a recording chamber and submerged in a continuously flowing artificial CSF (ACSF) solution (35°C, 2–3 ml/min) gassed with 95% O2/5% CO2. The composition of the ACSF solution was (in mM): 126 NaCl, 2.5 KCl, 1.2 MgCl2, 1.2 NaH2PO4, 2.4 CaCl2, 11 glucose and 25 NaHCO3. For whole-cell patch-clamp recordings, electrodes (4–5 M) were filled with a solution containing (in mM): 125 K+glucuronate, 10 NaCl, 1.0 CaCl2, 2.0 MgCl2, 0.5 1.2-bis (2-aminophenox)-ethane-N,N,N,N-tetra-acetic acid, 19 HEPES, 0.3 GTP and
1.0 Mg-ATP, adjusted to pH 7.3 with KOH. Striatal medium spiny neurons were selected by means of infrared videomicroscopy (Zeiss Axioskop, Jena, Germany) and a digital camera (Cohu, San Diego, CA, USA).

Recording pipettes were advanced towards individual cells in the slice under positive pressure, and on contact, tight GΩ seals were made by applying negative pressure. The membrane patch was then ruptured by suction and membrane current and potential monitored using an Axopatch 1D patch–clamp amplifier and Clampex 8.1 software (Axon Instruments, Foster City, CA, USA). Whole-cell access resistances measured in voltage clamp were in the range of 5–30 MΩ prior to electronic compensation (60–80% was routinely used). Striatal spiny neurons were clamped at −80 to −85 mV, close to their resting membrane potential to record spontaneous (sEPSCs) and evoked (eEPSCs) glutamate-mediated excitatory postsynaptic currents (EPSCs). These recordings were performed in the presence of 10 μM bicuculline to block GABA_A receptors. sEPSCs were analysed offline by MiniAnalysis 5.4.1 software (Synaptosoft, Decatur, GA, USA). To evoke EPSCs, bipolar electrodes were placed on corticostriatal fibres. In the experiments on paired-pulse facilitation the pulse interval was 40–60 ms. To evoke inhibitory GABAergic postsynaptic currents (IPSCs), the experiments were performed following intrastriatal stimulation in the presence of 10 μM 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX), an AMPA receptors antagonist, and 30 μM (+)-MK-801 maleate (MK-801), an NMDA receptors antagonist, by holding the recorded neuron at −40 mV.

Quantitative analysis
Quantitative data on modifications of eEPSCs and of IPSCs are expressed as a percentage of the controls, the latter representing the mean of responses recorded during a stable period (15–30 min) before the drug application. Values given in the text and figures are mean ± SD of changes in the respective cell populations. Wilcoxon’s test or Student’s t-test (for paired and unpaired observations) were used to compare the means. The concentration–response curves shown in the figures, and the concentration of inhibitor at 50% maximal inhibition (EC50s) were obtained using GraphPad Prism 3.0 software.

Drugs
Drugs were applied by dissolving them to the desired final concentration in Krebs’ solution and by switching the perfusion from control solution to drug-containing solution. CNQX, L-sulpiride and MK-801 were from Tocris-Cookson (Avonmouth, UK), 3,4-dihydroxyphenylalanine methyl ester (methyl-L-dopa), benzerazide, quinpirole, 6-OHDA, apomorphine and bicuculline-methiodide were from Sigma.

Results

Behavioural assessment following DA denervation and chronic l-dopa treatment
Previous studies have demonstrated that chronic l-dopa treatment, at the doses used in the present study, distinguishes two populations of subjects: those showing an anti-akinetic response to l-dopa in the absence of dyskinetic motor effects (therapeutic effect) and those showing no therapeutic benefit in response to l-dopa owing to the occurrence of dyskinesia (dyskinetic effect) (Cenci et al., 1998; Picconi et al., 2003).

In this study we selected the parkinsonian rats showing the therapeutic effects of l-dopa but no evidence of dyskinesia to analyse the electrophysiological modifications underlying the motor amelioration in this subgroup of animals. In this subgroup, treatment with l-dopa produced a complete recovery of lesion-induced motor alterations as detected by measuring both limb-use asymmetry behaviour and overall rotarod performance (Fig. 1A and B) (Rozas et al., 1997; Schallert et al., 2000; Picconi et al., 2003).

Quinpirole-induced modulation of evoked excitatory synaptic currents
Electrophysiological experiments were conducted in sham-operated rats, in 6-OHDA-lesioned rats and in 6-OHDA-lesioned rats after 13–21 days of l-dopa treatment. The intrinsic properties of striatal neurons, such as current-evoked firing discharge and the current–voltage relationship, did not significantly differ between these three experimental groups, and were similar to those previously reported for striatal spiny neurons recorded from control rats (Kita et al., 1984; Calabresi et al., 1990) (Fig. 2).
Corticostriatal eEPSCs were induced by a stimulating electrode placed in the white matter close to the recording electrode between the cortex and the striatum. To study the possible plastic modifications of DA receptors following DA denervation and chronic L-dopa treatment, we analysed eEPSCs from striatal spiny neurons in sham-operated rats, in 6-OHDA-lesioned animals and in 6-OHDA-denervated and L-dopa-treated rats. Previous studies have postulated an increase in the number of D2-like receptors after nigral lesion as a consequence of a variety of compensatory neurochemical changes (Fuxe and Ungerstedt, 1976; Schultz, 1982). Thus, we investigated the presynaptic modulation of glutamatergic transmission by quinpirole, a selective agonist of D2-like receptors in these three experimental groups.

As shown in Fig. 3A and B, quinpirole induced a significant dose-dependent inhibition of EPSCs evoked by corticostral stimulation in spiny neurons recorded from 6-OHDA-lesioned rats [n = 10; concentration at 50% maximal inhibition (EC50) = 1.8 μM; P < 0.001], but not in sham-operated rats (n = 11; P > 0.05). Interestingly, in the 6-OHDA-lesioned animals chronically treated with L-dopa, the inhibitory effect of quinpirole was abolished, suggesting that this treatment reverses the D2-like receptor hypersensitivity typical of parkinsonian rats (n = 12; P > 0.05).

We also performed a set of experiments to address the specific presynaptic effect of the D2-like receptor activation. eEPSCs were elicited by cortical fibre stimulation. Paired-pulse stimulations (40–60 ms interval) were delivered at 0.1 Hz, and eEPSCs were recorded throughout the whole experiment.

Paired-pulse modification of neurotransmission is attributed to a presynaptic change in release probability (Manabe et al., 1993; Schulz et al., 1994). An increase in the ratio of the second pulse response to the first pulse response (EPSC2/EPSC1) indicates a decrease in the release probability. The decrease in transmitter release is consistent with the observations that manipulations depressing transmitter release usually increase the magnitude of this ratio (Calabresi et al., 1997). Quinpirole (3 μM) induced a decrease in the amplitude of eEPSCs in spiny neurons recorded from 6-OHDA-lesioned rats. This effect of the drug was coupled with an increase in the eEPSC2/eEPSC1 ratio, indicating a clear presynaptic effect of the DA receptor agonist (Fig. 4A; n = 6 for each experimental group; P < 0.01). As shown in Fig. 4B, the effect of quinpirole was reversed by 3 μM L-sulpiride (n = 6).

In the group of lesioned animals that received the therapeutic L-dopa treatment, the effect of quinpirole on paired-pulse facilitation was reversed (n = 6; P > 0.05). Quinpirole, at the concentration tested in this study, did not affect resting membrane potential and input resistance of the neurons recorded in all the three experimental groups (data not shown).
Quinpirole-induced modulation of spontaneous glutamatergic activity

sEPSCs were also recorded from striatal spiny neurons. As shown in Fig. 5, the frequency and amplitude of sEPSCs recorded from spiny neurons of 6-OHDA-lesioned rats were significantly higher compared with sham-operated rats (n = 10 for each experimental condition) (Gubellini et al., 2002). The sEPSCs were suppressed by the application of 10 μM CNQX, an AMPA receptor blocker, confirming that these events were mediated by ionotropic glutamate receptors (not shown).

The pharmacological treatment with 3 μM quinpirole reduced sEPSC frequency in 6-OHDA-denervated rats, while no change was detected in either sham-operated animals or in denervated rats treated with l-dopa (Fig. 5D). The application of the D2-like agonist did not alter sEPSC amplitude in all three experimental groups (Fig. 5D).

Effect of quinpirole on GABA-mediated synaptic transmission

As it has been reported that activation of D2-like receptors exerts an inhibitory presynaptic effect not only on glutamate-mediated inputs, but also on striatal GABA-mediated synaptic transmission (Delgado et al., 2000; Centonze et al., 2002), we studied the effect of quinpirole on GABAergic IPSCs recorded from striatal spiny neurons in the three experimental groups. The application of the D2-like receptor agonist produced a dose-dependent inhibition of GABAergic IPSC amplitude showing similar characteristics in these three groups. In particular, the EC50 calculated for this effect was similar (Fig. 6A; n = 10 for each group; P > 0.05): 3.4 μM in...
slices from sham-operated rats, 5 µM in slices from 6-OHDA-lesioned rats and 4.9 µM in slices from 6-OHDA plus L-dopa-treated animals.

**Discussion**

L-dopa drastically improves the motor symptoms and the quality of life of Parkinson’s disease patients in the early stages of the disease. The improvement of motor symptoms by L-dopa is mandatory for the diagnosis of Parkinson’s disease (Rascol et al., 2003). However, the precise cellular and synaptic mechanisms underlying the therapeutic actions of L-dopa are not yet completely clear. A classical hypothesis postulates that L-dopa, after its conversion to DA, interacts with DA receptors and, by replacing endogenous DA, regulates a wide range of neuronal functions including motor activity. The electrophysiological data from the present study seem to suggest that L-dopa targets other neurotransmitter systems, such as glutamatergic overactive transmission. Accordingly, chronic interruption of nigrostriatal pathway causes plastic changes in glutamatergic transmission within the basal ganglia and alters the sensitivity of striatal D2-like DA receptors regulating glutamate release (Arnt and Hyttel, 1985). In this respect, mice lacking D2 receptors have a parkinsonian phenotype (Baik et al., 1995) and exhibit an increase in spontaneous glutamate events in the striatum, closely resembling the effects of DA denervation (Cepeda et al., 2001; Tang et al., 2001).

In the present study we have confirmed and extended our previous observation showing that parkinsonian animals express an increased spontaneous glutamatergic activity (Calabresi et al., 1993), and we have demonstrated that chronic L-dopa is able to ameliorate motor performances by restoring a physiological level of spontaneous excitatory inputs within the striatum.

A variety of compensatory neurochemical, morphological and behavioural alterations have been identified after 6-OHDA-induced striatal denervation (Schwarting and Huston,

![Fig. 5 Quinpirole-induced effect on sEPSCs of striatal spiny neurons of sham-operated rats, parkinsonian animals and L-dopa-treated parkinsonian rats.](http://brain.oxfordjournals.org/)

(A–C) Electrophysiological traces show glutamatergic sEPSCs from single cells pre- and post-quinpirole application under the three different experimental conditions. (D) The frequency of glutamatergic sEPSCs is increased in 6-OHDA-lesioned animals, and their amplitude. L-dopa treatment in parkinsonian rats restores both sEPSC frequency and amplitude to sham-operated levels. The D2-like receptor agonist reduces sEPSC frequency in 6-OHDA-denervated animals. This effect, when normalized, is similar in sham-operated animals, 6-OHDA-lesioned rats and in 6-OHDA-denervated rats chronically treated with L-dopa. Conversely, the amplitude of sEPSCs is not significantly affected by the drug application in the three experimental groups of animals (n = 10 for each condition; *P < 0.01 versus sham-operated rats, Student’s t-test).
Pharmacological blockade or genetic ablation of the D2-like receptors, also resulted in reduced terminal arbor (Parish et al., 2003). All these findings can be explained either by assuming that a nigrostriatal lesion induces modifications of sensitivity of D2-like DA receptors or by postulating that the DA denervation alters the coupling between DAergic receptors with their transduction mechanisms.

Unilateral DA denervation also causes the loss of the corticostriatal synaptic plasticity (Centonze et al., 1999; Calabresi et al., 2000). We have recently shown that in a large subgroup of parkinsonian animals the same therapeutic dose of L-dopa used in the present study restored physiological corticostriatal synaptic plasticity and induced motor improvement. In ~50% of the parkinsonian rats, however, this regimen of L-dopa treatment caused abnormal involuntary movements and altered the reversal of corticostriatal long-term potentiation, suggesting abnormal synaptic plasticity in the pathogenesis of L-dopa-induced dyskinesia (Picconi et al., 2003). We also found that the activation of D2-like receptors by quinpirole induces a presynaptic inhibition of glutamatergic transmission in slices obtained from parkinsonian rats, but not in control slices (Calabresi et al., 1993), while a novel finding of the present study is the reversal of the presynaptic inhibitory effect of quinpirole by therapeutic L-dopa treatment. Similar results are observed in parkinsonian rats that exhibit dyskinetic behaviour in response to L-dopa treatment. However, preliminary data from our laboratory seem to suggest that dyskinetic animals show a decreased glutamatergic eEPSC (unpublished data). This issue requires further experimental investigation.

It has been shown that although L-dopa treatment does not protect or rescue nigrostriatal DAergic fibres (Camp et al., 2000; Ishida et al., 2000), it partially restores striatal DAergic transmission and exerts a trophic effect repairing the ultrastructural changes in the corticostriatal pathway caused by the denervation (Ingham et al., 1998).

The inhibition of glutamatergic transmission by quinpirole in DA-depleted animals is mediated by a presynaptic mechanism. Two experimental findings support this idea. First, the inhibition exerted by quinpirole is coupled to an increase of paired-pulse facilitation. This electrophysiological phenomenon has been extensively correlated to a presynaptic site of action (Manabe et al., 1993; Schulz et al., 1994). Secondly, the analysis of sEPSCs has shown that quinpirole reduces the frequency of these events. This finding also strongly suggests a presynaptic effect for this drug.

In vivo neurochemical studies have shown that 6-OHDA-induced DA denervation increases striatal basal or stimulated GABA release (Lindefors et al., 1989). The increased GABA release following DA denervation may be due to the loss of DA-mediated inhibition of local GABAergic striatal neurons. This plastic alteration suggests that experimental parkinsonism not only alters the excitatory transmission, but also modifies striatal GABAergic inhibitory tone. We have been unable to detect significant changes in the efficacy and in the potency of quinpirole in inhibiting GABA-mediated striatal IPSCs following denervation. This finding indicates that, at

Fig. 6 Equal presynaptic inhibitory effect of quinpirole in GABAergic IPSCs in sham-operated rats, in 6-OHDA-denervated rats and in 6-OHDA-lesioned rats plus L-dopa treatment. (A) The graph shows the dose-dependent curves obtained for the inhibitory effect of the D2-like receptor agonist in the three different experimental conditions (n = 10 for each condition; P > 0.05). (B) Electrophysiological traces of IPSCs recorded before and during drug application in sham-operated rats, in 6-OHDA-lesioned rats and in 6-OHDA rats plus L-dopa treatment.
least in vitro, the sensitivity of D2-like receptor controlling GABA release is unchanged after this procedure. It is possible, however, that in the sensitivity of D2-like receptors inhibiting GABA release within the striatum would be detected by utilizing an in vivo electrophysiological approach. Moreover, we found that also chronic L-dopa treatment failed to affect D2-like receptor-mediated presynaptic inhibition of GABAergic synaptic currents in DA-denervated rats.

Here we have shown that, in animals showing a motor improvement following chronic L-dopa treatment, restoration of DA levels might represent a way to compensate the pathological adaptive changes triggered by DA denervation such as the enhanced sensitivity of presynaptic inhibitory D2-like receptors and the abnormal striatal glutamatergic excitatory transmission.

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