Neurobiology of Disease 35 (2009) 376–384

Contents lists available at ScienceDirect

Neurobiology of Disease

journal homepage: www.elsevier.com/locate/ynbdi

D2 receptor stimulation, but not D1, restores striatal equilibrium in a rat model of Parkinsonism

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ARTICLE INFO

Article history:
Received 14 April 2009
Revised 26 May 2009
Accepted 28 May 2009
Available online 6 June 2009

Keywords:
Levodopa
Quinpirole
Striatum
Electrophysiology
Dopamine
Parkinson's disease
Striatonigral
Striatopallidal
GABA interneuron

ABSTRACT

In Parkinson's disease dopamine depletion imbalances the two major output pathways of the striatum. L-DOPA replacement therapy is believed to correct this imbalance by providing effective D1 and D2 receptor stimulation to striatonigral and striatopallidal neurons, respectively. Here we tested this assumption in the rat model of Parkinsonism by monitoring the spike response of identified striatal neurons to cortical stimulation. As predicted, in 6-hydroxydopamine lesioned rats we observed that L-DOPA (6 mg/kg + benserazide), apomorphine and the D2 agonist quinpirole (0.5 mg/kg i.p.) counteract the enhanced responsiveness of striatopallidal neurons. Unexpectedly, the depressed responsiveness of striatonigral neurons was corrected by quinpirole whereas D1 stimulation exerted no (apomorphine, cPB) or worsening effects (L-DOPA, SKF38393 10 mg/kg). Therefore, quinpirole, but not D1 stimulation, restores functional equilibrium between the two striatal output pathways. Our results might explain the therapeutic effect of D2-based medications in Parkinson's disease.

Introduction

According to pathophysiological models of Parkinson's disease, the dopamine depletion results in an imbalanced activity of projection neurons in the striatum, which is responsible for the hypokinesia associated with this disease (Albin et al., 1989; Bezard et al., 2001; DeLong, 1990). Dopamine replacement therapy by L-DOPA is thought to alleviate parkisonian motor symptoms by correcting this striatal imbalance.

In the rat striatum, medium sized spiny neurons (MSNs) represent 95% of the neurons. MSNs are GABAergic projection neurons and belong to two populations. Striatonigral neurons form the direct pathway to substantia nigra pars reticulata (SNR) and express substance P and D1 dopamine receptors. Striatopallidal neurons initiate the indirect pathway and express enkephalin (ENK) and D2 receptors (Gerfen and Wilson, 1996). According to anatomical (Deng et al., 2006; Gerfen et al., 1990; Hersch et al., 1995; Le Moine and Bloch, 1995) and genetic (Day et al., 2006; Gantois et al., 2007) studies in rodents, D1 and D2 receptor colocalization is restricted to about 5% of the MSNs.

In the rat model of Parkinson's disease the striatal imbalance caused by dopamine depletion has been documented by anatomo-functional studies (Gerfen, 2000; Gerfen et al., 1990) and directly demonstrated by our electrophysiological study (Mallet et al., 2006). Indeed, using in vivo electrophysiological recordings of identified neurons, we showed that striatonigral neurons and striatopallidal neurons exhibit similar sensitivity to cortical stimulation in intact rats (Mallet et al., 2005). In contrast, in the striatum of rats rendered hemiparkinsonian by 6-hydroxydopamine (6-OHDA) injection in the medial forebrain bundle, we observed that both the spontaneous activity and the sensitivity to cortical stimulation of striatonigral neurons decreased, but the opposite effects were induced in striatopallidal neurons (Mallet et al., 2006).

Based on anatomo-functional studies, pathophysiological models of parkinsonian treatments posit that the stimulation of D1 receptors by L-DOPA or D1 agonists counteracts the depressed activity of striatonigral neurons and that stimulation of D2 receptors reverses the overactivity of striatopallidal neurons (Gerfen, 2000; Gerfen et al., 1990). Indeed, systemic treatments with L-DOPA and D1 agonists dramatically increase the expression of immediate early genes specifically in striatonigral neurons in the dopamine-depleted striatum (Carta et al., 2005; Gerfen et al., 1995, 2002; Robertson et al., 1990). Conversely, the dopamine depletion enhances the ENK mRNA (Gerfen et al., 1990) and the mRNA level of *zif268* specifically in striatopallidal

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doi:10.1016/j.nbd.2009.05.019

neurons (Gerfen et al., 1995). These increases are reversed by quinpirole, a D2 agonist (Gerfen et al., 1990, 1995). However, changes in anatomo-functional markers do not necessarily reflect parallel changes in electrophysiological activities (Sgambato et al., 1999). This is an important issue because the latter are more directly related to pathological dysfunctions than the former. Here we used the same electrophysiological approach as previously (Mallet et al., 2006) to test whether systemic treatments with L-DOPA and dopaminergic agonists actually correct the striatal imbalance caused by the dopamine depletion. Although in vivo investigations with systemic treatments have obvious limitations regarding mechanistic descriptions, they must be done to provide therapeutically relevant information.

Methods

Animals

Experiments were carried out with male Sprague–Dawley rats in accordance with European Council Directive 86/609/EEC guidelines for the care of laboratory animals and were approved by the Ethical Committee of CNRS, Région Aquitaine. Seven week old rats (240–280 g) were injected with 6-OHDA in the medial forebrain bundle 3–4 weeks before electrophysiological recordings as described (Mallet et al., 2006). The effectiveness of the lesion was asserted with tyrosine hydroxylase immunoreactivity (Mallet et al., 2006). The dopaminergic lesion was considered sufficient when the number of TH positive cell bodies in the substantia nigra pars compacta ipsilateral to the 6-OHDA injection was decreased by at least 90% compared with the contralateral side.

Electrophysiological recordings

Rats were anesthetized with urethane at a dose (1.2 to 1.6 g/kg, i.p.) sufficient to abolish any movement response to tail pinch, and single neurons were extracellularly recorded from the rostrolateral striatum, as described (Mallet et al., 2005). Briefly, glass pipettes (8–15 MΩ) simultaneously recorded spike discharges and the striatal local field potentials as described (Mallet et al., 2005). In urethane-anesthetized rats the dominant cortical state exhibits a rhythmic activity characterized by slow waves of large amplitude at a frequency close to 1 Hz. This cortical slow wave state induces in the striatum parallel slow oscillations of the striatal field potential (Mallet et al., 2005). In all experiments described here the striatal field potential was continuously monitored to assert that the recorded animal was actually in the slow wave state. If disruption of the slow waves spontaneously occurred, the slow wave state was restored with additional i.p. injection of urethane (15% of the initial dose). Antidromic stimulation of the SNR was used to identify MSNs (Mallet et al., 2005). Concentric bipolar electrodes (SNEX-100, Rhodes Medical Instruments, Summerland, CA 93067, USA) were implanted in the rostral pole of ipsilateral SNR (2.4 mm to medial line, 4.9 mm caudal to bregma and 8.0 below the cortical surface). Striatonigral neurons exhibited antidromic responses to SNR stimulation and were named SNR+. Antidromic responses fulfilled the following criteria: (1) constant latency of spike response, (2) all-or-none property of the spike response when the strength of the stimulation was adjusted just above, or just below, threshold, and (3) collision of the antidromic spikes with orthodromic spikes. Because all SNR+ MSNs were silent in 6-OHDA-lesioned rats, the orthodromic spike required for the collision test was evoked by electrical stimulation of the orofacial motor cortex (Mallet et al., 2006). We named SNR− the neurons, which did not exhibit the features of striatal interneurons and which did not exhibit antidromic responses to SNR stimulation (Mallet et al., 2006). Striatal neurons were considered to be unresponsive to antidromic stimulation of the SNR if they exhibited no antidromic spike response to SNR stimulation at maximal current (1.2 mA) while, in the same experiment, at least one SNR+ neuron was identified by a SNR stimulation at a current ≤0.5 mA. Moreover, all but two of the 47 SNR− neurons recorded here in 6-OHDA-lesioned rats were spontaneously active. The two silent SNR− neurons were not further studied.

In order to test the dynamic response of MSNs to cortical input we used paired cortical stimulations at 100 ms intervals as described (Mallet et al., 2006) and we measured the probability of spike discharges in response to both pulses. In order to preserve the

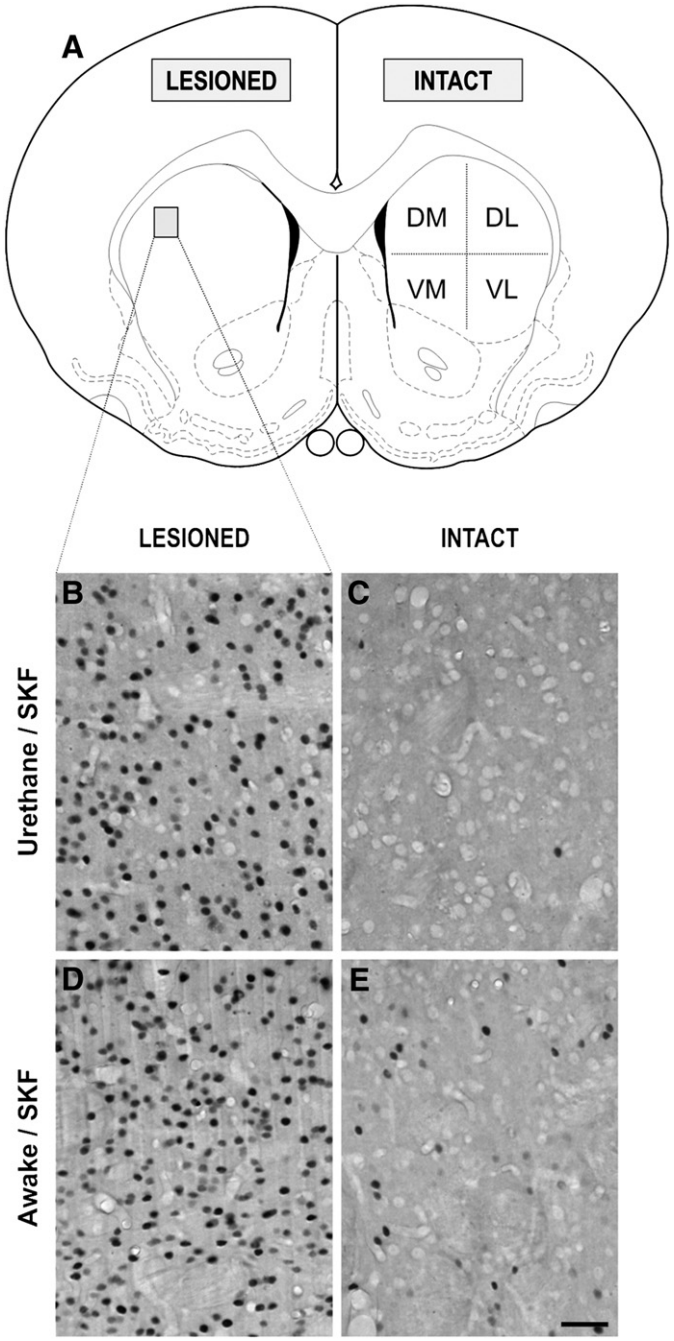

Fig. 1. Fos immunoreactivity in the dorsolateral striatum in the 6-OHDA-lesioned and intact sides of urethane-anesthetized or awake rats, 2 h following saline or D1 agonists treatments. (A) The number of Fos-positive neurons was counted in the four quadrants (DL: dorsolateral, DM: dorsomedian, VL: ventrolateral, VM: ventromedian) of both lesioned and intact striatum. Because we observed no major differences in the drug effects between the four striatal quadrants, the figure shows only micrographs obtained in the dorsolateral striatum. (B–E) Photomicrographs illustrating the effect of SKF-38393 (5 mg/kg, i.p.) on the Fos immunoreactivity observed in the lesioned striatum (B, D) and the intact striatum (C, E) of one rat anesthetized with urethane (B, C) and one awake rat (D, E). Scale bar = 50 μm.

efficiency of the cortical stimulation throughout experiments the stimulating current was limited to a maximum of 800 μA. Drugs were purchased from Sigma-Aldrich (Lyon, France) and were administered i.p. only once per rat: L-DOPA methyl ester hydrochloride (6 mg/kg), benserazide hydrochoride (15 mg/kg), R-(−)-apomorphine hydrochloride hemihydrate (0.2 mg/kg), (±)-SKF-38393 (5 and 10 mg/kg), (±)-6-Chloro-PB hydrobromide (cPB) (0.5 mg/kg) and (−)-quinpirole hydrochloride (0.5 mg/kg). Drug effects were measured after injections at time ranges that correspond to the maximum of their behavioral effects in 6-OHDA-lesioned rats (Fletcher and Starr, 1989; LaHoste and Marshall, 1990; Lundblad et al., 2002; Ruskin et al., 1999).

Anatomo-functional experiments

The effects of two D1 agonists, SKF-38393 (5 mg/kg, i.p.) and cPB, 0.5 mg/kg, i.p.), on the number of c-Fos-positive neurons were compared to saline treatment in 6-OHDA-lesioned rats either under urethane anesthesia or in awake freely moving rats. Anesthetized rats were fixed on a stereotaxic frame, sham-operated and their slow wave activity was continuously monitored. Saline or D1 agonists were administered to anesthetized rats 4 h after induction of anesthesia. Awake rats were gently moved from their home cage to an individual circular chamber and allowed to habituate for 30 min before either saline or D1 agonist injection. Two hours after drug treatments all rats were sacrificed, under deep urethane anesthesia, by intracardiac perfusion, via the ascending aorta, with sodium chloride (NaCl 9‰) at 4 °C for 5 min followed by 250 ml of a 4% paraformaldehyde (PFA) solution at 4 °C prepared in a 0.2 M phosphate buffer (pH = 7.2). Free-floating serial coronal vibratome sections (60 μm thick) at the striatal level (between 1.60 mm and −0.26 mm from Bregma according to Paxinos and Watson (1997)) were then collected and preserved in 0.01 M PBS at pH = 7.2 containing 0.03% sodium azide at 4 °C until use.

C-Fos immunohistochemistry

C-Fos immunohistochemistry was performed following a procedure slightly modified from Frenois et al. (2007). Briefly, sections were rinsed in 0.01 M PBS at pH = 7.2 for 10 min, then placed in 0.01 M PBS (pH = 7.2) containing 30% sucrose for 1 h before being fast frozen in isopentane cooled at −40 °C with liquid nitrogen and directly immersed in PBS at room temperature. After rinsing (0.01 M PBS at pH = 7.2, 2 × 5 min), sections were pre-incubated in 0.01 M PBS (pH 7.2)/1.5% Triton X100/3% normal donkey serum under agitation for 1 h at room temperature. Sections were then incubated overnight at room temperature under agitation with the anti-c-Fos primary antibody (sc52, Santa Cruz Biotechnology, California, USA), diluted 1/8000 in 0.01 M PBS (pH 7.2)/0.3% Triton X100. The following day, sections were rinsed (0.01 M PBS, pH = 7.2, 3 × 10 min) and incubated under agitation during 2 h at room temperature with a biotinylated donkey anti-rabbit secondary antibody (Amersham Biosciences, Freiburg, Germany) diluted 1/200 in PBS 0.01 M (pH = 7.2). Sections were rinsed in 0.01 M PBS (pH = 7.2) 3 × 10 min then incubated 90 min under agitation at room temperature in the ABC complex (Vector Laboratories, Peterborough, UK) diluted 1/200 in 0.01 M PBS at pH = 7.2. After rinsing (PBS 0.01 M, pH = 7.2, 2 × 10 min), sections were put into 1× TBS (pH = 7.6; 3 × 5 min), before being revealed by diaminobenzidine (0.2 mg/ml) diluted in 1× TBS pH = 7.6, in the presence of nickel (40 mg/ml) and 0.3% H_2O_2 (which catalyses the reaction). Sections were then rinsed into 1× TBS, pH = 7.6 (2 × 5 min) and into distilled water (2 × 5 min), then spread out over slides, air dried then and mounted in Eukitt.

Analysis of c-Fos experiments

The number of c-Fos immunoreactive nuclei was counted using an image analyzer system for cartography (Mercator, Explora Nova, La Rochelle, France) within the entire striatum divided in four quadrants: dorsomedial (DM), dorsolateral (DL), ventromedial (VM) and ventrolateral (VL) (see Fig. 1A). For all rats, quantification was performed within the 6-OHDA-lesioned as well as in the intact striatum. Statistical analysis was performed on individual raw data using a two-way analysis of variance (ANOVA) followed by *post-hoc* Bonferroni/Dunn multiple comparison test.

Results

Anatomo-functional studies under urethane anesthesia

Systemic administration of D1 agonists much more strongly stimulates the expression of immediate early genes in the 6-OHDA-lesioned striatum than in the intact striatum (Gerfen et al., 1995, 2002; Robertson et al., 1989, 1990). Because these enhanced expressions are largely restricted to striatonigral neurons (Gerfen et al., 1995, 2002; Robertson et al., 1990), these observations have brought strong support to the view that D1 stimulation corrects the depressed activity of striatonigral neurons caused by the dopamine depletion. The first aim of our study was to test whether electrophysiological approaches also support this view. However, because we had to identify MSNs by means of antidromic SNR stimulation, our electrophysiological experiments were performed under urethane anesthesia. Therefore, as a preliminary step, we verified that urethane anesthesia does not alter the anatomo-functional data. As previously reported, in awake freely moving rats the D1 agonists SKF-38393 and cPB strongly stimulated c-Fos expression in the 6-OHDA-lesioned striatum but induced much smaller effects in the intact striatum (Fig. 1 and Table 1). In experimental conditions identical to those of our electrophysiological studies (rats sham-operated under urethane anesthesia) these D1

Table 1
D1 agonist-induced Fos-like immunoreactivity in freely moving and urethane-anesthetized rats with unilateral 6-OHDA lesion.

	Freely moving		Urethane-anesthetized		*F* value (2-way ANOVAs)	
	Saline	D1 agonist	Saline	D1 agonist	Motor state	Treatment
SKF-38393	$n=5$	$n=6$	$n=5$	$n=5$		
Intact DL-STR	9 ± 5	69 ± 20	2 ± 1	1 ± 1		
Lesioned DL-STR	51 ± 13	1691 ± 329	14 ± 4	1398 ± 201	0.59	49.99
Intact VL-STR	1 ± 1	91 ± 22	0 ± 1	1 ± 1		
Lesioned VL-STR	14 ± 6	1668 ± 335	12 ± 4	1111 ± 127	1.87	45.56
cPB	$n=5$	$n=3$	$n=5$	$n=5$		
Intact DL-STR	8 ± 2	61 ± 31	7 ± 6	6 ± 4		
Lesioned DL-STR	46 ± 6	1136 ± 418	26 ± 4	1421 ± 272	0.41	36.62
Intact VL-STR	5 ± 3	76 ± 35	2 ± 1	5 ± 3		
Lesioned VL-STR	39 ± 11	1013 ± 322	6 ± 2	1458 ± 325	0.93	32.34

Data are mean ± SEM and represent numbers of Fos-positive nuclei per mm^2. Two-way ANOVAs demonstrate significant effects of drug treatment with SKF-38393 (5 mg/kg, i.p.) and cPB (0.5 mg/kg, i.p.) in the dorsolateral striatum (DL-STR) and the ventrolateral striatum (VL-STR) ($p<0.0001$), but no significant effect of motor state (freely moving versus anesthetized) ($p \geq 0.10$). Post hoc tests indicate significant Fos induction by both D1 agonists compared to vehicle treatment in the lesioned striatum in both motor states ($p<0.0001$).

agonists also strongly stimulated c-Fos expression in the 6-OHDA-lesioned striatum but not in the intact striatum (Fig. 1 and Table 1). Similar increases were observed in both lateral quadrants of the 6-OHDA-lesioned striatum, which corresponded to the localization of the electrophysiological recordings (Table 1) and also in both medial quadrants (data not shown). Preliminary experiments with SKF-38393 at the dose of 10 mg/kg (three 6-OHDA-lesioned rats under urethane anesthesia) gave similar results (data not shown).

Corticostriatal transmission in identified MSNs

As in our previous study we identified here four types of striatal neurons (Mallet et al., 2006). Tonically active neurons were identified by their unique, regularly spaced, spontaneous activity between 2 and 6 Hz. These neurons were presumed to be cholinergic interneurons and were not further studied here. Fast spiking GABA interneurons (FSI) were identified by their spike duration, which is briefer than that of all other striatal neurons, and by the fact that they respond with brief burst of 2 to 5 action potentials to supra threshold cortical stimulation (Mallet et al., 2005, 2006). As previously, neurons, which exhibited antidromic responses to SNR stimulation (Fig. 2) were named SNR+ and were considered to be striatonigral MSNs in accordance with previous studies (Ballion et al., 2008; Jaeger et al., 1994; Mallet et al., 2005, 2006; Ryan et al., 1986, 1989). Finally, we named SNR− those neurons, which did not correspond to interneurons and which did not exhibit antidromic responses to SNR stimulation. We previously showed with double labeling that these neurons express the mRNA coding for ENK, a recognized feature of striatopallidal neurons (Mallet et al., 2006). Moreover, we previously observed that, in the 6-OHDA-lesioned striatum, SNR− MSNs are much more spontaneously active than in intact rats, whereas the opposite effect was observed regarding SNR+ neurons (Mallet et al., 2006). Accordingly, all 71 SNR+ neurons studied here in 6-OHDA-lesioned rats were spontaneously silent. In contrast, all but two of the 47 SNR− MSNs studied here were spontaneously active (range: 0.02 to 2.12 Hz; mean ± SD: 0.62 ± 0.58 Hz). Both silent SNR− MSNs were discarded because they might correspond to striatonigral neurons not detected by the antidromic SNR stimulation.

We tested the spike responses evoked in MSNs by pairs of cortical stimulations applied at 100 ms time intervals. We previously showed in intact rats that the feedforward inhibition by FSIs more dramatically affects the spike responses evoked in MSNs by the first pulse than by the second pulse (Mallet et al., 2005). In 6-OHDA-lesioned rats striatopallidal neurons are more responsive to cortical stimulation and tend to escape this feedforward inhibition. In contrast, the cortical response of striatonigral neurons is depressed by the dopamine depletion and this deficit is worsened by feedforward inhibition, especially the response to the first pulse (Mallet et al., 2006). Indeed, in intact rats the current required to evoke a spike response to the second pulse with a 50% probability was almost identical for SNR+ and SNR− neurons (395 ± 24 μA $n = 73$ and 385 ± 21 μA $n = 76$, respectively) (Ballion et al., 2008). Here, in 6OHDA-lesioned rats, this current was enhanced for SNR+ neurons (540 ± 24 μA, mean ± SEM $n = 71$) and decreased for SNR− MSNs (349 ± 22 μA, mean ± SEM $n = 45$). The difference between SNR+ and SNR− neurons is highly significant (unpaired t test, $p < 0.0001$). Therefore, the present data

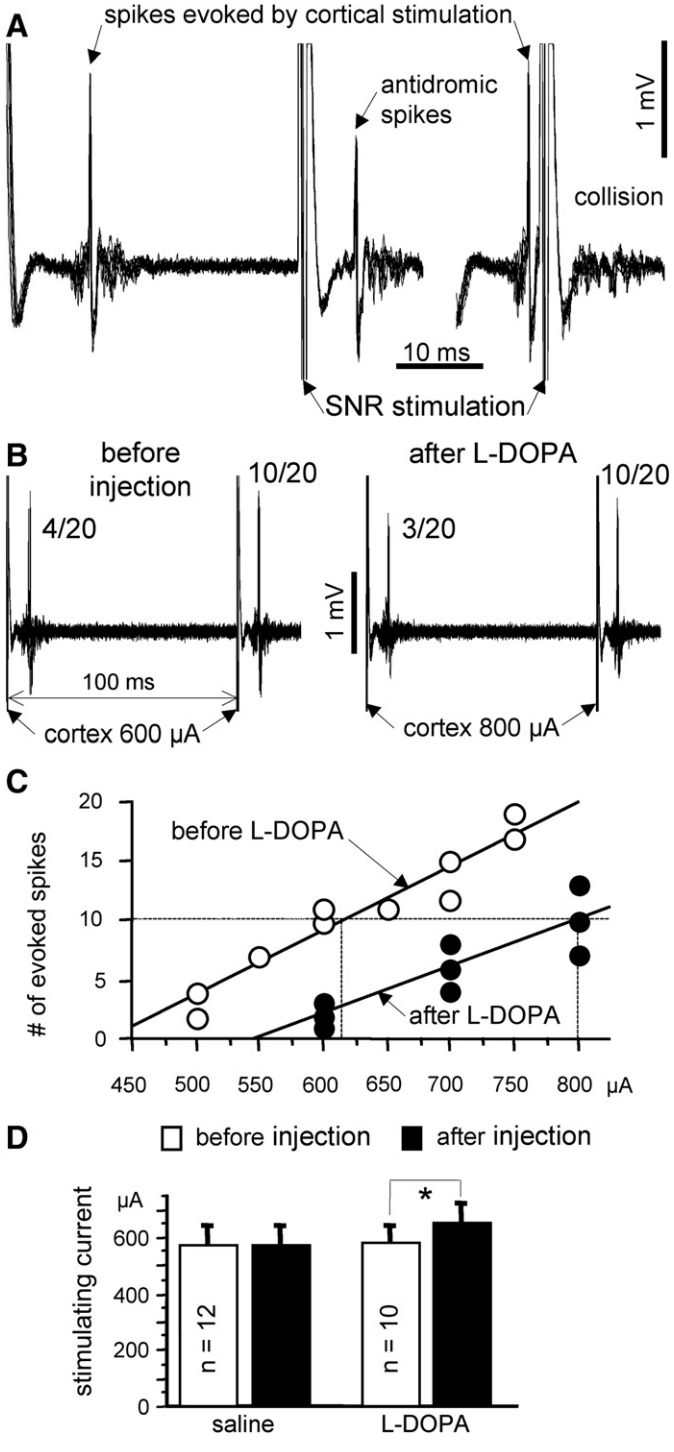

Fig. 2. Effect of L-DOPA on the spike response of SNR+ MSNs to cortical stimulation. (A) Anitdromic identification of one SNR+ neuron. The stimulation of the substantia nigra pars reticulata (SNR) was triggered by an orthodromic spike evoked by cortical stimulation with a time interval of 25 ms (left) or 1 ms (right). Recordings show the superimposition of 10 successive responses to SNR stimulation in both conditions. Notice the fixed latency of the antidromic spikes (left) and the collision of the orthodromic spike with the antidromic one at 1 ms intervals (right). Only neurons that fulfilled the 3 criteria of an antidromic response (see Methods) were considered to be striatonigral and called SNR+. (B) Typical example of spike responses evoked in one SNR+ neuron before and after L-DOPA injection. Pairs of cortical stimulations at 100 ms intervals were applied every 3 s by groups of 20 pairs. The spike responses to various stimulations were tested in current ranges, which allowed us to explore in every neuron the full probability scale both before and 30 to 45 min after L-DOPA injection (6 mg/kg + benserazide 15 mg/kg, i.p.). Examples of recordings show the superimposition of the spike responses to cortical stimulations at currents, which evoked a 50% probability in response to the second pulse before (left) and after L-DOPA (right). (C) Number of spikes evoked in the SNR+ neurons illustrated in B in response to the second pulse of the paired cortical stimulation at distinct currents before (white circles) and 30–45 min after L-DOPA (black circles). As illustrated, linear regression allowed us to determine for every neuron the current required for evoking a spike response to the second pulse with a 50% probability before and after L-DOPA or saline injection. (D) Stimulating current required for evoking a spike response with a 50% probability, before and after saline ($n = 12$) or L-DOPA ($n = 10$) injections. Bar histograms (mean ± SEM) show that L-DOPA significantly inhibited the spike responses evoked in SNR+ neurons by the second pulse of the cortical stimulation (paired t test, $^*p = 0.048$).

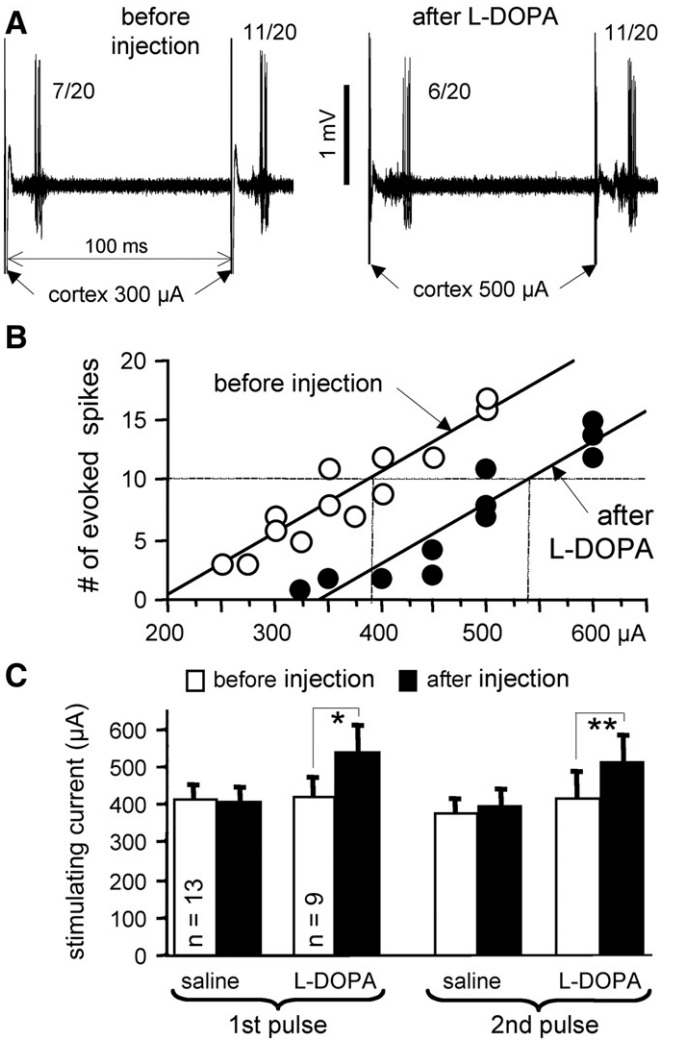

Fig. 3. Effect of L-DOPA on the spike response of SNR− MSNs to cortical stimulation. (A) Typical examples of spike responses evoked in one SNR− neuron before and after L-DOPA injection. Pairs of cortical stimulations at 100 ms intervals were applied every 3 s by groups of 20. The spike responses to various stimulations were tested in current ranges, which allowed us to explore in every neuron the full probability scale both before and 30 to 45 min after L-DOPA injection (6 mg/kg + benserazide 15 mg/kg, i.p.). Examples of recordings show the superimposition of the spike responses to cortical stimulations at currents, which evoked a 50% probability in response to the second pulse before (left) and after L-DOPA (right). (B) Number of spikes evoked in the SNR− neuron illustrated in A in response to the first pulse of the paired cortical stimulation at distinct currents before (white circles) and 30–45 min after L-DOPA (black circles). Linear regression allowed us to determine for every neuron the current required for evoking a spike response to the first and second pulses with a 50% probability before and after L-DOPA or saline injection. (C) Stimulating current required for evoking a spike response with a 50% probability, before and after saline ($n=13$) or L-DOPA ($n=9$) injections. Bar histograms (mean ± SEM) show that L-DOPA significantly inhibited the spike responses evoked in SNR− neurons by the first pulse (paired t test, $^{*}p=0.010$) and by the second pulse of the cortical stimulation (paired t test, $^{**}p=0.004$).

confirm the striatal imbalance described in our previous study (Mallet et al., 2006). Moreover, as in our previous study (Mallet et al., 2006), we found here numerous MSNs, which responded to SNR stimulation in an antidromic manner (fixed latency and all-or-none responses at stimulating currents just above or below threshold), but which did not respond to cortical stimulation at maximal current (800 μA). Thus, it is likely that identified SNR+ neurons, which responded to cortical stimulation, already represented a subpopulation of striatonigral neurons. Among them, about a third responded to the second pulse but their response to the first was too low to be quantified. Therefore, in experiments with drug treatments that inhibit the cortical response of SNR+ neurons, we only considered the spike responses evoked by the second pulse.

Effect of L-DOPA and apomorphine on the spike responses of identified MSNs

In control experiments with saline injections the responsiveness of SNR+ (Fig. 2) and of SNR− (Fig. 3) neurons to cortical stimulation was fairly stable with time. Compared to saline treatment, L-DOPA significantly inhibited the spike response evoked by the second pulse in SNR+ neurons (ANOVA with repeated measures, $F=5.09$ $p=0.035$) (Fig. 2). In SNR− neurons (Fig. 3) L-DOPA treatment, compared to saline, also significantly inhibited the spike response evoked by the first pulse (ANOVA with repeated measures; $F=14.54$ $p=0.001$) and the second pulse (ANOVA with repeated measures; $F=6.69$ $p=0.017$). Moreover, L-DOPA moderately depressed the spontaneous discharge activity of SNR− neurons (0.43 ± 0.18 Hz after L-DOPA versus 0.57 ± 0.21 Hz before injection, mean ± SEM, paired t test: $p=0.045$ $n=9$), whereas this activity was fairly stable after saline injection (0.61 ± 0.20 Hz before injection versus 0.63 ± 0.19 Hz after injection, mean ± SEM, $n=13$). Finally, L-DOPA did not restore the spontaneous activity of SNR+ neurons.

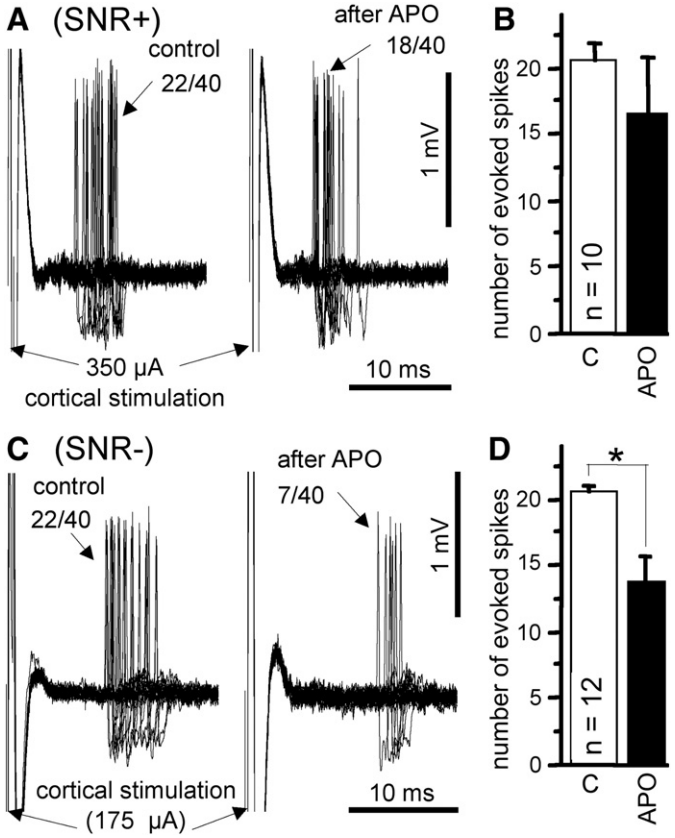

Fig. 4. Effect of apomorphine (0.2 mg/kg i.p.) on the spike response of identified MSNs to cortical stimulation. (A) Typical examples of spike responses evoked in one SNR+ neuron. Pairs of cortical stimulations at 100 ms intervals were applied every 3 s by group of 40. The stimulating current was adjusted by preliminary tests so that the response probability to the second pulse reached 50% before drug injection. Recording traces show the superimposition of the spike responses to the second pulse either before (control) or 20 min after apomorphine injection. (B) Bar histograms (mean ± SEM, $n=10$) show that apomorphine did not significantly affect the discharge probability of SNR+ neurons. (C) Typical examples of spike responses evoked in one SNR− MSN. Stimulation conditions were as described in B and recordings show the superimposition of the spike responses to the second pulse either before (control) or 20 min after apomorphine injection. (D) Bar histograms (mean ± SEM, $n=12$) show that apomorphine significantly depressed the discharge probability of SNR− MSNs in response to cortical stimulation (paired t test, $p=0.008$).

Apomorphine, a mixed D1–D2 agonist, did not significantly affect the spike response evoked by the second pulse of the cortical stimulation in SNR+ neurons and significantly decreased it in SNR− MSNs (Fig. 4). Apomorphine also decreased the spike response evoked by the first pulse in the 12 SNR− MSNs studied (paired t test, $p = 0.002$; data not shown) and did not affect this response in 7 of the 10 SNR+ neurons (data not shown). In the 3 other SNR+ neurons we were not able to study the spike response to the first pulse because the response probability at maximal stimulating current (800 μA) was below 50%.

Effects of D1 agonists on SNR+ neurons

In 6-OHDA-lesioned rats SKF-38393 at the dose of 10 mg/kg significantly depressed the probability of the spike response evoked in SNR+ neurons by the second pulse of paired cortical stimulations (Fig. 5A). SKF-38393 at a lower dose (5 mg/kg) and cPB (0.5 mg/kg) has no significant effect on this spike response either in intact or in 6-OHDA-lesioned rats (Fig. 5B). Among the 25 SNR+ neurons tested in 6-OHDA-lesioned rats and which were responsive to the second pulse, 19 were also responsive to the first pulse at a stimulating

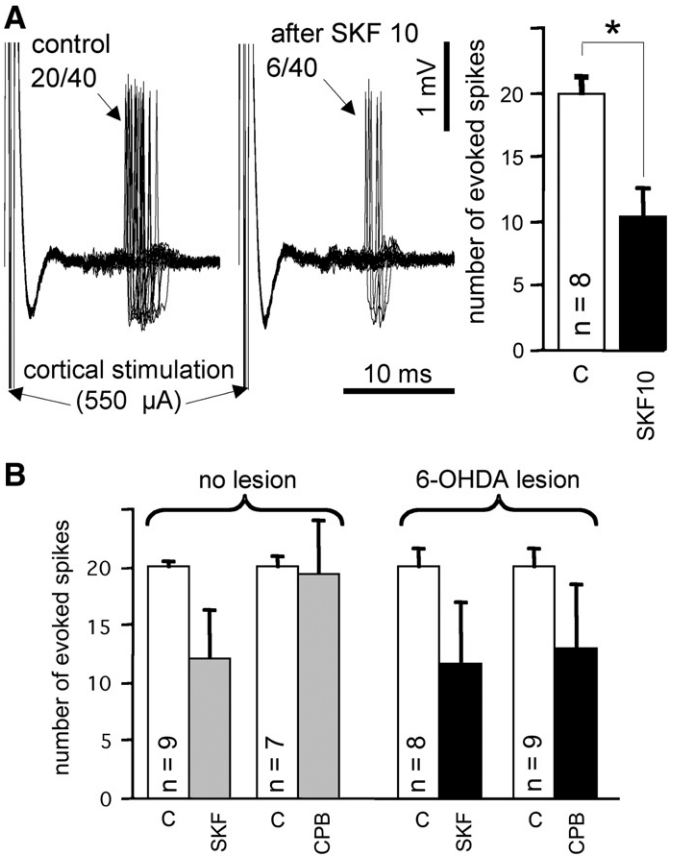

Fig. 5. Effect of D1 agonists on the discharge probability of SNR+ neurons. (A) Typical examples of spike responses evoked in one SNR+ MSN recorded in a 6-OHDA-lesioned rat. Pairs of cortical stimulations at 100 ms intervals were applied every 3 s by group of 40. The stimulating current was adjusted by preliminary tests so that the response probability to the second pulse reached 50% before drug injection. Recordings show the superimposition of the spike responses to the second pulse either before (control) or 30 min after SKF-38393 injection at the dose of 10 mg/kg. Bar histograms (mean ± SEM, $n = 8$) show that SKF-38393 (10 mg/kg) significantly depressed the discharge probability of SNR+ neurons recorded in 6-OHDA-lesioned rats (paired t test, $p = 0.003$). (B) In the same experimental conditions the effects of SKF-38393 (5 mg/kg) and of cPB (0.5 mg/kg) on the discharge probability of SNR+ neurons were studied in 16 intact rats ($n = 9$ and $n = 7$, respectively) and 17 6-OHDA-lesioned rats ($n = 8$ and $n = 9$, respectively). Bar histograms (mean ± SEM, number of experiments indicated inside bars) show that these treatments tended to depress the discharge probability of SNR+ neurons. However, these effects never reached statistical significance (paired t test, $p > 0.1$).

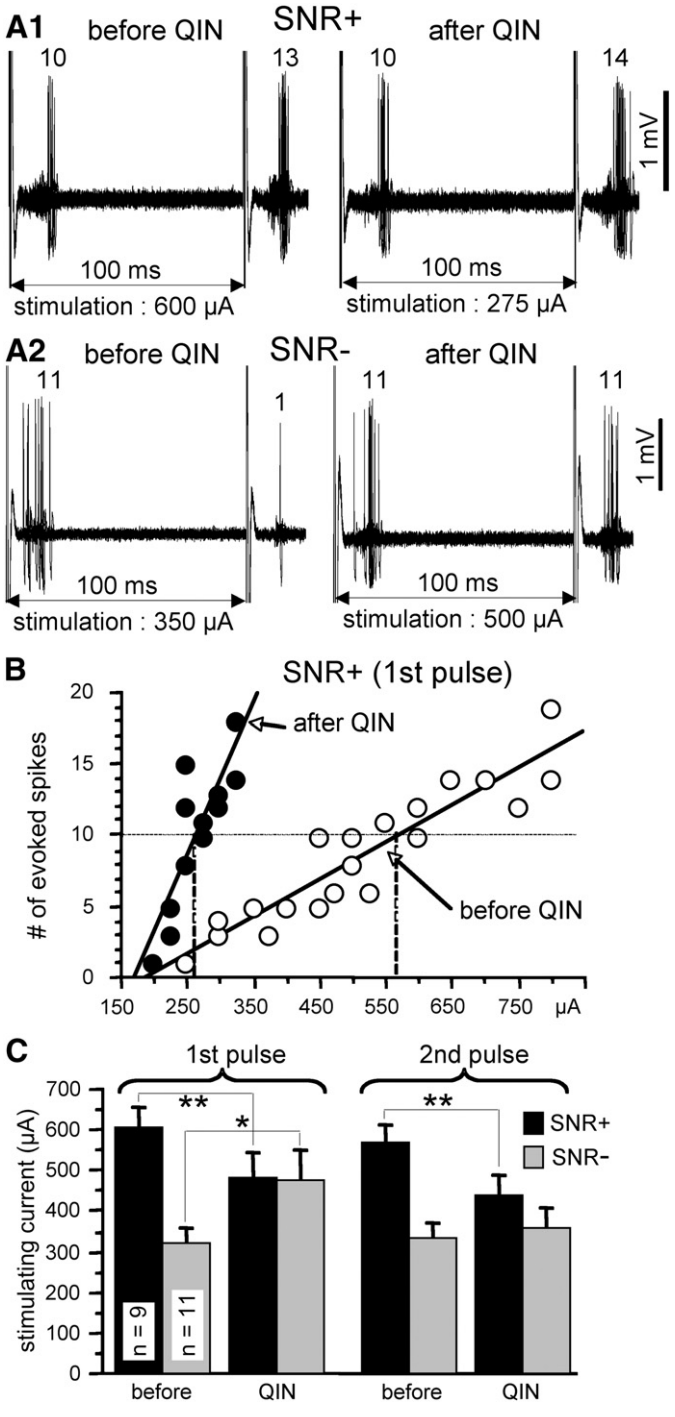

Fig. 6. Effects of quinpirole (QIN, 0.5 mg/kg) on the discharge probability of SNR+ and SNR− MSNs. (A) Typical examples of spike responses evoked in one SNR+ MSN (A1) and one SNR− MSN (A2). Pairs of cortical stimulations at 100 ms intervals were applied every 3 s by group of 20. The spike responses to various stimulations were tested in current ranges, which allowed us to explore in every neuron the full probability scale both before and 20 to 40 min after quinpirole injection. Examples of recordings show the superimposition of the spike responses to cortical stimulations at currents, which evoked a 50% probability in response to the first pulse before (left) and after quinpirole (right). (B) Number of spikes evoked in the SNR+ illustrated in A1 in response to the first pulse of the paired cortical stimulation at distinct currents before (white circles) and 20–40 min after quinpirole (black circles). Linear regression allowed us to determine for every neuron the current required for evoking a spike response with a 50% probability for the first and second pulses, before and after quinpirole. (C) Stimulating current required for evoking a spike response with a 50% probability, before and after quinpirole. Bar histograms (mean ± SEM) show that quinpirole significantly facilitated the spike responses evoked in 9 SNR+ neurons by the first and second pulses of the cortical stimulation (paired t test, $^{**}p < 0.0076$) and significantly inhibited the spike responses evoked in 11 SNR− MSNs by the first pulse of the cortical stimulation (paired t test, $^{*}p = 0.011$).

current ≤800 μA. SKF-38393 at doses of 5 and 10 mg/kg and cPB (0.5 mg/kg) did not significantly affect their response to the first pulse (data not shown).

Effects of quinpirole on identified MSNs and on FSIs

As expected, the D2 agonist quinpirole (0.5 mg/kg) inhibited the spike responses evoked in SNR− MSNs by the first and second pulses of paired cortical stimulations. Indeed, the stimulating current required to evoke a spike response with a 50% probability was increased by quinpirole injection. However, this increase reached statistical significance regarding the spike response evoked by the first pulse but not by the second pulse (Fig. 6). To our surprise quinpirole facilitated the spike responses evoked in SNR+ neurons by the first and second pulses. Indeed, the stimulating current required for evoking a spike response with a 50% probability was significantly decreased after quinpirole treatment (Fig. 6). This facilitation was even more robust when considering 3 additional SNR+ neurons, which only responded to the second pulse. Indeed, when considering all these 12 SNR+, the stimulating current required for evoking a spike response to the second pulse was significantly decreased (data not shown, paired t test, $p=0.0036$). When comparing SNR+ to SNR− neurons before quinpirole treatment (Fig. 6C), we observed that the stimulating current required to evoke a spike response with a 50% probability was significantly higher for the former than for the latter both regarding the first pulse (unpaired t test, $p=0.0002$) and the second pulse (unpaired t test, $p=0.0008$). After quinpirole injection we observed no significant differences regarding these currents (Fig. 6C). Therefore, quinpirole reinstates equilibrium between striatonigral and striatopallidal MSNs with regard to their responsiveness to cortical input.

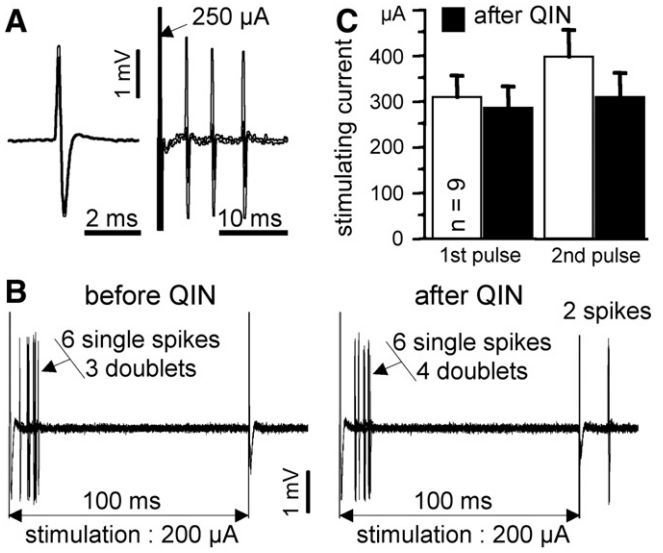

Fig. 7. Effect of quinpirole (QIN, 0.5 mg/kg) on the spike response of fast spiking GABA interneurons (FSI) to paired cortical stimulations. (A) FSI were identified by their spike waveform, which is sharper than that of MSNs, and by their burst responses to supra threshold stimulations. (B) Spike responses evoked by paired cortical stimulation in the FSI identified in A before and after quinpirole injection. Pairs of cortical stimulations at 100 ms intervals were applied every 3 s by group of 20. The spike responses to various stimulations were tested in current ranges, which allowed us to explore in every FSI the full probability scale both before and 20 to 40 min after quinpirole injection. Examples of recordings show the superimposition of the spike responses to cortical stimulations at currents, which evoked a 50% probability in response to the first pulse before (left) and after quinpirole (right). The stimulating current required for evoking a spike response with a 50% probability, before and after quinpirole was determined by means of linear regression as illustrated in Fig. 6B. (C) Bar histograms (mean ± SEM, $n=9$) show that quinpirole did not significantly affect the spike responses evoked in FSI by the first and second pulses of the cortical stimulation (paired t test, $p=0.34$ and $p=0.051$, respectively).

Because FSI exert a potent feedforward inhibition on MSNs, we also investigated the effect of quinpirole on the spike response of FSIs to paired cortical stimulation. As illustrated in Fig. 7A, FSI were identified by their thin spike waveform and their ability to discharge with bursts to supra threshold stimulations. However, we found that quinpirole did not significantly affect the spike responses of the 9 FSI studied (Fig. 7) suggesting that the effects observed in MSNs are not related to drug-induced changes in feedforward inhibition.

Discussion

In accordance with anatomo-functional studies in the rat model of Parkinson's disease (Gerfen, 2000; Gerfen et al., 1990) we show here with our electrophysiological approach that D2 stimulation reverses the enhanced responsiveness of striatopallidal neurons to cortical stimulation. However, regarding striatonigral neurons, two important and unexpected findings resulted from our study. First, L-DOPA and D1 agonists do not counteract, and even worsen, their depressed response to cortical stimulation caused by the dopamine depletion. Second, the D2 agonist quinpirole robustly reverses this depressed response, reinstating a functional equilibrium between striatal output neurons.

Choice of a dynamic index to test corticostriatal transmission

The imbalance of striatal projection neurons caused by the dopamine depletion is well documented by anatomo-functional data (Gerfen, 2000; Gerfen et al., 1990) and by our electrophysiological study (Mallet et al., 2006). In urethane-anesthetized rats this imbalance is obvious both with regard to the spontaneous activity and the spike responses evoked by cortical stimulation. Indeed, in intact rats the spontaneous activity of MSNs is low and very irregular but in 6-OHDA-lesioned rats it is dramatically enhanced specifically in striatopallidal neurons. Although L-DOPA and D2 agonists effectively alleviate parkinsonian symptoms, L-DOPA (present study) and quinpirole (Zold et al., 2007) only moderately reversed (−25% and −28%, respectively) the enhanced spontaneous activity of striatopallidal neurons. However, the spontaneous discharge rate is a tonic parameter, whereas the spike response to cortical stimulation represents a dynamic index, which might be more relevant to movements, especially in the context of the pathophysiology of Parkinson's disease (Leblois et al., 2006). Therefore, we investigated here the spike responses evoked in identified MSNs by cortical stimulation and we used the paired pulse protocol that we previously developed (Mallet et al., 2006).

D2 stimulation, but not D1, corrects the striatal imbalance

To our surprise, we found that stimulation of D1 receptors by L-DOPA, apomorphine, SKF-38393 (5 mg/kg) or cPB did not correct, and actually further worsened (L-DOPA, SKF-38393 10 mg/kg), the depressed response of striatonigral neurons to cortical stimulation in 6-OHDA-lesioned rats. In contrast, the same drug treatments strongly enhance the expression of immediate early genes specifically in striatonigral neurons of the 6-OHDA-lesioned striatum (Carta et al., 2005; Gerfen et al., 1990, 1995, 2002; Paul et al., 1995; Robertson et al., 1990). This discrepancy is not related to our experimental conditions because we observed that D1 agonists induced almost identical stimulations of c-Fos expression in awake rats and in urethane-anesthetized rats. Likewise, barbiturate anesthesia did not affect these D1-mediated stimulations of c-Fos expression (Robertson et al., 1989). Although the mismatch we observe here between early gene expression and discharge activity was not expected, a similar mismatch has been previously reported regarding the discharge and immediate early gene responses of SNR neurons to cortical stimulation (Sgambato et al., 1999). According to Sgambato et al. (1999)

"changes in gene expression induced in the basal ganglia reflect the level of afferent synaptic activity rather than the spike discharge of postsynaptic neurons". Moreover, our data showing that striatonigral neurons are further inhibited by D1 agonists are in line with a previous electrophysiological study. Indeed, striatonigral neurons are GABAergic and inhibit the discharge activity of SNR neurons (Kita, 1994; Maurice et al., 1999). However, SKF-38393 and cPB, at doses that induce contralateral rotation and strongly stimulate c-Fos expression in the 6-OHDA-lesioned striatum, did not affect the discharge rate of SNR neurons (Ruskin et al., 1999). Therefore, from this previous study it seems unlikely that D1 stimulation strongly enhances the discharge activity of striatonigral neurons in the 6-OHDA-lesioned striatum. Our data are consistent with this prediction.

As predicted by the pathophysiological model of parkinsonian treatment, we found that L-DOPA, apomorphine and the D2 agonist quinpirole depressed the enhanced responsiveness of striatopallidal neurons. Unexpectedly, quinpirole also reversed the depressed responsiveness of striatonigral neurons. This facilitatory effect of quinpirole is highly significant both regarding the spike responses evoked by the first and second pulses. These changes cannot be due to an indirect action of quinpirole on FSI activity because we observed that dopamine depletion (Mallet et al., 2006) and subsequent quinpirole treatment did not affect their responsiveness to cortical input. However, presynaptic D2 receptors exert an inhibitory control on GABA transmissions from MSN collaterals and from FSI terminals to individual MSNs (Delgado et al., 2000; Tecuapetla et al., 2007). Therefore, quinpirole might improve the responsiveness of striatonigral MSNs by inhibiting their GABAergic inputs at a level downstream from spike generation. Further studies with in vitro approaches are required to clarify the effects of quinpirole on striatonigral neurons. Taken all together, the differences in the response of striatonigral and striatopallidal neurons to cortical stimulation, which express the functional imbalance caused by the striatal dopamine depletion, are abolished by quinpirole treatment.

Therapeutical implications

Replacement therapy with L-DOPA remains the mainstay of Parkinson's disease treatment. However, long-term L-DOPA therapy is associated, in most patients, with treatment-related involuntary movements known as L-DOPA-induced dyskinesia (LID) (Hauser et al., 2007; Horstink et al., 2006a; Horstink et al., 2006b; Schapira, 2007). In 6-OHDA-lesioned rats with a severe dopamine depletion the first injection of L-DOPA induces abnormal involuntary movements (Lindgren et al., 2007). Clinical and experimental studies point out the role of D1 receptors in the initiation and maintenance of LID (Cenci, 2007; Rascol et al., 2001). More precisely, numerous experimental studies have implicated the hypersensitivity of striatal D1 receptors in LID and assumed that striatonigral neurons are hyperactive during LID (Bezard et al., 2001; Brotchie et al., 2005; Cenci, 2007; Gerfen et al., 2002). However, only a few electrophysiological studies backed this assumption. They showed that LID is associated with a decrease of the firing rate and with changes in the dynamic properties of neurons recorded in the SNR or other output nuclei of the basal ganglia (Boraud et al., 2001; Meissner et al., 2006). However, the causal relationship between these pathological activities and a hypothetical increase in the discharge activity of striatonigral neurons has not been established. Our study shows that, in the severely depleted striatum, D1 stimulation either did not reverse or even worsened (L-DOPA and SKF 38393 at 10 mg/kg) the functional inhibition of striatonigral neurons while the same treatments strongly stimulate their molecular activity (Carta et al., 2005; Gerfen et al., 1995, 2002; Robertson et al., 1990). This functional inhibition might be causally linked to the expression of LID. Indeed, selective lesion of striatonigral neurons in mice also induces the appearance of abnormal involuntary movements (Gantois et al., 2007).

Monotherapy with D2 agonists is efficient in the early stages of Parkinson's disease and is increasingly used because it reduces the incidence of motor complications as compared to L-DOPA therapy (Horstink et al., 2006a; Schapira, 2007). However, in advanced Parkinsonism, D2 agonist treatment is often associated with L-DOPA therapy. This combined treatment is superior to L-DOPA monotherapy because it significantly decreases the incidence of motor fluctuations and LID (Hauser et al., 2007; Horstink et al., 2006b). Indeed, compared to L-DOPA monotherapy, lower doses of L-DOPA can be used with the combined treatment and motor complications are positively related to the duration and doses of L-DOPA treatment (Hauser et al., 2007; Horstink et al., 2006b). However, the mechanisms underlying these D2-based treatments are still debated. Our observations might shed a new light to this question. Indeed, parkinsonian pharmacotherapy is mainly aimed at restoring a dopaminergic stimulation of striatal neurons. However, in healthy subjects physiological dopaminergic functions are achieved by two distinct modes of dopamine release: i) a tonic release, which is generated by the tonic discharge activity of dopaminergic neurons and which mainly stimulates high affinity D2 receptors, and ii) a larger phasic release, which results from brief bursts of dopaminergic action potentials and which transiently stimulates D1 receptors in their low affinity state (Gonon et al., 2000; Goto et al., 2007; Richfield et al., 1989). In the early stage of Parkinsonism, the tonic D2 stimulation achieved by D2 agonists might compensate for the decrease of the tonic dopamine release. We showed here that this D2 stimulation is sufficient to restore a functional equilibrium between both striatal projection pathways. However, this tonic D2 stimulation does not restore the phasic dopaminergic transmission. In the early stages an efficient phasic release might be achieved by surviving dopaminergic neurons providing that D2 agonists could correct the striatal imbalance. In more advanced Parkinsonism, low doses of L-DOPA might help the few surviving dopaminergic neurons to achieve a sufficient phasic transmission in a striatum whose imbalance is already corrected by D2 agonists. Therefore, our study calls for a re-examination of the functional state of striatal projection neurons during chronic treatments with L-DOPA and D2 agonists.

Acknowledgments and funding

We thank Drs Thomas Boraud and Martin Guthrie for critical reading of the manuscript and Jean-Gabriel Hervouet and Laura Cardoit for technical assistance. This work was supported by the Centre National de la Recherche Scientifique, the University of Bordeaux and 'La Fondation de France' (B.B., F.F. and F.G.), by Secretaría de Ciencia, Tecnología e Innovación Productiva, Fondo para la Investigación Científica y Tecnológica (PICT 26323), Universidad de Buenos Aires and Consejo Nacional de Investigaciones Científicas y Técnicas (Argentina) (C.Z. and M.G.M.). Collaboration between the two groups was funded by International Cooperation Program SECyT-ECOS (A05S01, France and Argentina).

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