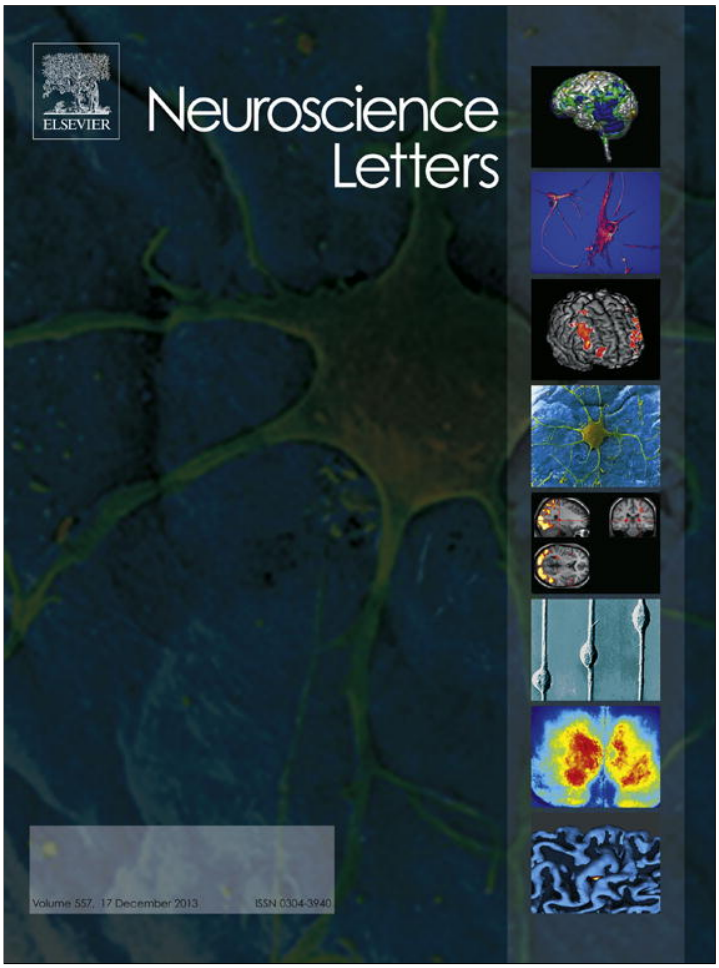

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Remodeling of the dendritic structure of the striatal medium spiny neurons accompanies behavioral recovery in a mouse model of Parkinson's disease

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HIGHLIGHTS

- MPTP-treated mice showed impaired motor behavior but made spontaneous recovery.
- Changes in dendritic structure of MSNs were correlated with the behavioral changes.
- Rasagiline significantly increased the dendritic complexity of MSNs in culture.

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ABSTRACT

Medium spiny neurons (MSNs) are the major type of neurons found in the striatum. The dendritic spines on these cells contain glutamatergic synaptic contacts between the cortex (or the thalamus) and the striatum. The complexity of the dendritic structure of MSNs may therefore reflect the functional status of the basal ganglia because the striatum is the major input structure in which signals from different regions are integrated. We examined the structural alterations in the dendrites of striatal MSNs in an 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced mouse model of Parkinson's disease (PD). Acute MPTP treatment rapidly damaged dopaminergic neurons and their terminals within the striatum and caused behavioral impairments. However, mice injected with MPTP spontaneously recovered from these behavioral impairments within one week. This recovery was accompanied by the restoration of dendritic structures on MSNs, but the damage to dopaminergic neurons remained extensive. Furthermore, we demonstrated that rasagiline, a monoamine oxidase-B (MAO-B) inhibitor that has been shown to be efficacious for PD, could enhance the dendritic complexity of cultured MSNs. The effect of rasagiline on the spine-like structures of dendrites, however, appears not to require DA availability because the small protrusions of dendrites in cultured MSNs without major source of DA input was similarly changed by rasagiline. Our data suggest that the dendritic structures of striatal MSNs change dynamically, reflecting the progression of motor-related symptoms in PD, and the restoration of functional synapses in the MSNs of PD patients may constitute a clinical target for symptomatic alleviation.

1. Introduction

Parkinson's disease (PD) is a neurodegenerative disease that is characterized by dramatic loss of dopaminergic neurons in the substantia nigra pars compacta (SNc), of which major projections make synapses onto medium spiny neurons (MSN) of the striatum [1]. The lack of dopamine (DA) in the striatum is regarded as a major cause of motor-related PD symptoms, such as tremors, bradykinesia, and postural instability, because the striatum is the main gateway to the basal ganglia, a group of interconnected subcortical nuclei that are crucial for motor planning. DA inputs are

Abbreviations: PD, Parkinson's disease; DA, dopamine; MSN, medium spiny neuron; SNc, substantia nigra pars compacta; VTA, ventral tegmental area; MAO, monoamine oxidase; TH, tyrosine hydroxylase.

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precisely localized to the necks of the dendritic spines of MSNs while the excitatory glutamatergic input from the cortex contacts the spine heads [8]. This synaptic configuration allows dopamine to efficiently modulate the effects of excitatory glutamatergic inputs to MSNs. In fact, perturbations in the DA system can lead to changes in glutamatergic synaptic transmission and plasticity in the striatal MSNs [6,7].

Plastic changes in dendritic morphology are closely correlated with the dynamic functional state of related synapses and, to some extent, with the overall network properties. In addition, the dendritic structure of MSNs is altered in some abnormal conditions. For example, treatment with psychostimulants, which increases extracellular DA levels in animal models of drug addiction, has been shown to enhance dendritic branching [14]. In contrast, overexpressing the dopamine D2 receptors (D2Rs) in MSNs decreases the extent of dendritic arborization [6]. Post-mortem studies of idiopathic PD have reported dendritic atrophy and a reduction in the density of dendritic spines in MSNs [19,21]. Similar dystrophic changes in the dendritic structures of MSNs have been induced by depleting dopamine in the striatum of the animal models of PD [10]. Together, these findings suggest that changes in the dendritic structure of MSNs may play a crucial role in mediating the motor-related symptoms of PD and therefore that modulating dendritic structures may be an important means of improving the living conditions of PD patients.

In the present study, we examined whether changes in dendritic structure of striatal MSNs are correlated with symptomatic alterations in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced mouse model of PD. Our data indicate that the behavioral recovery in MPTP-lesioned mice is accompanied by the restoration of the dendritic structures in striatal MSNs. In addition, we show that rasagiline, an inhibitor of monoamine oxidase B (MAO-B), could increase the structural complexity of dendrites in cultured MSNs.

2. Materials and methods

2.1. Animals

Animal experiments were performed using male C57BL/6N mice (Orient Bio, Seoul, Korea) that were 9–10 weeks of age at the time of experiments. Animals were allowed to acclimate in a climate-controlled room with 12-h light-dark cycle (lights on at 07:00 am) for at least one week prior to the start of MPTP injections. Water and food were provided *ad libitum*. All animal experiments were carried out in accordance with the Laboratory Animal Care and Use Committee of Korea University. All efforts were made to minimize animal suffering and to reduce the number of animals used. For acute MPTP administration, four intraperitoneal (IP) injections of 20 mg/kg MPTP (free base) were performed with two-hour intervals.

2.2. Primary neuronal cell culture

Embryos from a pregnant SD rat were harvested at 16.5 days of gestation for dissociated cultures. The striatum and the midbrain were micro-dissected out in the presence of ice-cold dissection buffer. Finely chopped tissues were treated with papain at 37 °C for up to 40 min and triturated to dissociate the cells. Approximately, 0.6×10^6 cells (60% striatum + 40% midbrain or 100% striatum) were plated onto a 60 mm dish with 3 glass coverslips (18 mm) in 5 ml media. Rasagiline (1 μM) or vehicle (DMSO) was added to the culture on day 1 *in vitro* (1 DIV) and 20% of the media was replenished daily with media containing fresh drug.

2.3. Immunocytochemistry

To visualize neurons, adeno-associated virus (AAV) vector expressing YFP was added to cultured neurons at 7 DIV, and the cells were fixed (4% paraformaldehyde, 4% sucrose in PBS) 24 h later. Cells were rinsed with PBS containing 0.02% Na-Azide for 10 min and were placed in blocking buffer (10% FBS, 0.1% Triton-X, 0.02% Na-Azide in PBS) for 1 h. Cells were then incubated with a primary antibody against a rabbit DARPP-32 (Cell Signaling) at 1:400 dilution overnight at room temperature. After washing with PBS containing 0.02% Na-Azide for 10 min, cells were incubated with a secondary antibody at 1:400 dilution (goat anti-rabbit IgG-Alexa546, Invitrogen) for 2 h at room temperature. Cells were rinsed with PBS containing 0.02% Na-Azide (3× 10 min) and they were mounted on glass slides using VECTASHIELD H1000 (Vector laboratories).

2.4. Immunohistochemistry

The assessment of neuronal loss in the substantia nigra (SN) was made by analyzing serial sections (30 μm) prepared from bregma −3.08 mm to bregma −3.20 mm. Brain slices were incubated with blocking buffer (5% normal horse serum, 0.1% bovine serum albumin, 0.3% Triton X-100 in 0.1 M PBS) for 1 h and then incubated with a rabbit anti-tyrosine hydroxylase (TH) antibody (Millipore) at 1:400 dilution overnight at 4 °C. The sections were subsequently incubated with secondary antibody at 1:400 dilution (goat anti-rabbit IgG-Alexa546, Invitrogen) for 1 h at room temperature and rinsed before mounting. Stereological analyses were conducted using Olympus IX71 and Image Pro Plus software (Media Cybernetics). The average fluorescence intensity of each region from 4 sections per animal was obtained.

2.5. Slice preparation and DiI-coated biolistic labeling

After sacrifice, the brain was quickly removed and transferred to ice-cold high sucrose dissection buffer (in mM, 87 NaCl, 2.5 KCl, 1.25 NaH_2PO_4, 25 $NaHCO_3$, 1 $CaCl_2$, 3 $MgCl_2$, 10 dextrose, and 75 sucrose) bubbled with carbogen (5% CO_2 and 95% O_2). Coronal slices (200 μm thick) were prepared using a vibratome. All slices were rinsed with PBS once and then fixed in 4% paraformaldehyde in PBS. Fixed brain slices were placed on a 1.5% agarose block for biolistic labeling. Tungsten particles (1 μm diameter) were first coated with DiI solution (Molecular Probes, 0.0125 mg/ml dissolved in methyl chloride), and 25 mg of the DiI-coated tungsten particles were then used to coat the inner wall of Tefzel tubing. The tungsten particles were applied to the fixed slices at 100 psi helium pressure. The slices were washed in PBS before mounting.

2.6. Imaging and dendritic structure analyses

All DiI-labeled cells that had clear soma and spiny dendrites were chosen for imaging. Images were taken using a confocal fluorescence microscope (ZEISS LSM 700 META), while the experimenter was blind to the condition of treatment. Z-Stacks were acquired using a 0.099 μm × 0.099 μm × 0.343 μm voxel size on an inverted Carl Zeiss LSM 700 confocal microscope equipped with a Plan-Apochromat 63x/1.40 oil immersion objective. Dendritic spine analysis was performed using NeuronStudio (http://research.mssm.edu/chic/tools-ns.html) as described previously [15]. All spine-like protrusions, branch points, and dendritic length were measured per cell, and the total measurements were divided by the total number of concentric circles (shell) to obtain average number per shell. Protrusions under 3.0 μm and over 0.2 μm in length were considered as spine-like protrusions. The criteria for the morphological classification of spines

were as follows: thin spines, spine length (L)/head diameter (d_h) ≥2.5 (except for the spines that meet the criterion for mushroom spines); mushroom spines, d_h/neck diameter (d_n) > 1.1, $d_h \geq 0.35\,\mu m$; stubby spines, $L/d_h < 2.5$, $d_h < 0.35\,\mu m$. All image analyses were performed in a blind fashion.

2.7. Behavioral analyses

2.7.1. Open field test (OFT)

The OFT was performed to measure the overall locomotor activity of animals. Movement within an open field chamber (30 cm × 30 cm) was video-recorded under dim light for 30 min. The video tracking analysis was performed using Ethovision XT (Noldus).

2.7.2. Pole test

The pole test was performed as previously described [11] with minor modifications. The pole was gauze-wrapped for gripping (50 cm height, 1 cm diameter). The mouse was placed head-upward near the top of the pole. The time for an animal to turn downward from the top and to descend to the floor was measured. The test was performed under dim light.

2.8. Statistical analysis

Data were analyzed with one-way ANOVA followed by Tukey's *post hoc* multiple comparison test as appropriate. All data are expressed as the mean ± standard error of the mean (SEM). Statistical analyses were carried out using SPSS20.

3. Results

3.1. Naturally occurring behavioral recovery is correlated with the restoration of dendritic structure in striatal MSNs

It has been documented that both the behavioral and the neurochemical changes induced by acute MPTP treatment can be reversible [17]. Indeed, our acute MPTP administration produced significant impairments in motor behavior as measured by the open field test and the pole test 2 days after MPTP injection (MPTP2D).

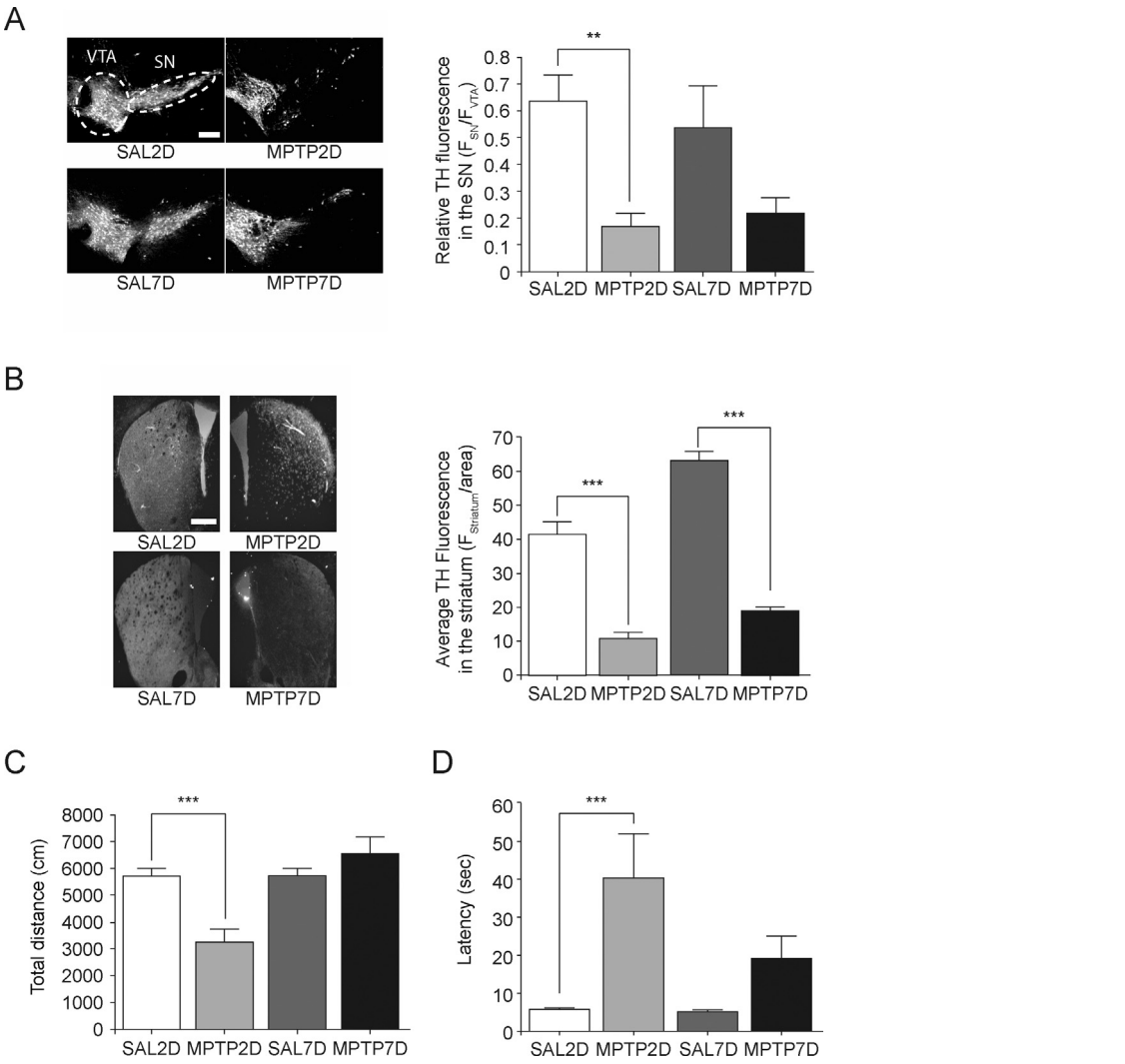

Fig. 1. Acute MPTP administration to C57/BL6N mice induces the loss of TH-positive DA cells and behavioral impairment that can be recovered within a week. (A) Representative images of TH-stained SN and VTA (left panel) and quantified results of relative TH fluorescence intensity within the SN (right panel). Total fluorescence intensity within the SN (F_{SN}) was normalized to total fluorescence intensity within the VTA (F_{VTA}) (SAL2D, $n = 6$; MPTP2D, $n = 6$; SAL7D, $n = 4$; MPTP7D, $n = 4$). (B) Representative images of TH staining in the dorsal striatum (left panel) and average TH fluorescence intensity of the dorsal striatum (normalized to area of dorsal striatum, right panel) (SAL2D, $n = 6$; MPTP2D, $n = 10$; SAL7D, $n = 8$; MPTP7D, $n = 8$). (C) Total distance that each mouse traveled in the open field for 30 min (SAL2D, $n = 14$; MPTP2D, $n = 17$; SAL7D, $n = 10$; MPTP7D, $n = 10$). (D) Latency of each mouse to land down to the ground in the pole test (SAL2D, $n = 28$, MPTP2D, $n = 28$, SAL7D, $n = 24$, MPTP7D, $n = 23$). Asterisks indicate different p-values ($^{**}p < 0.01$, $^{***}p < 0.001$). Scale bars indicate 500 μm.

However, when the MPTP-lesioned animals were tested for the same tasks one week later, their behavioral impairments were largely ameliorated (MPTP7D) (Fig. 1C, D). The observed recovery is not entirely due to the neurochemical restoration, since MPTP-lesioned mice still exhibited extensive loss of dopaminergic neurons and their terminals 1 week after MPTP administration (Fig. 1A, B).

We next analyzed the dendritic structure and spine morphology of striatal MSNs in the MPTP-lesioned mice. The structure and distribution of dendritic spines could reflect the functional status of a neuron or a neural network [2]. The number of dendritic spines and the dendritic length were significantly decreased when they were measured 2 days after acute injections of MPTP (Fig. 2). The number of branch points also decreased upon MPTP administration when compared to that from saline-injected controls (SAL2D), but this effect failed to reach statistical significance (SAL2D *vs.* MPTP2D, $p = 0.052$). However, when we examined the dendritic structures 1 week after acute MPTP administration, the number of spines, the dendritic length, and the number of branch points had all recovered to levels comparable to those observed in saline-injected controls (SAL7D). We also compared the number of concentric shells used for each cell in our Sholl analysis. In addition to the dendritic length per shell, the number of shells per cell was significantly higher in the MPTP7D group than in other groups (SAL2D, 128.18 ± 4.32; MPTP2D, 128.67 ± 5.20; SAL7D, 132.60 ± 4.83; MPTP7D, 149.83 ± 4.37). Morphological analyses of dendritic spines revealed that a reduction in spine numbers was observed in all three types of spines and that behavioral recovery was accompanied by the restoration of all three types of spines.

We realized that the loss of TH-positive axon terminals within the striatum was not consistent throughout the dorsal striatum. Our regional TH analysis revealed that the dorsolateral quadrant of the caudate putamen is less susceptible to the loss than other quadrants. We considered a possibility that differential DA denervation might have biased our data considering that it has been shown that the extent of striatal spine loss is linked with the degree of DA denervation [20], despite the fact that the neurons analyzed were randomly distributed in all quadrants without any bias. Therefore, we reanalyzed a subset of samples (that were randomly chosen) with excluding the neurons in the dorsolateral quadrant. We found that the length of dendrites in MPTP7D group was not recovered. However, the number of spines was still significantly increased in MPTP7D group (Fig. 2F).

3.2. Rasagiline remodels dendritic structure in cultured striatal neurons

We examined whether rasagiline could affect dendritic structures or spine structures in normal cultured MSNs in order to assess the possibility of the drug efficacy being partly due to its potency to regenerate the dendritic spines of MSNs. When rasagiline was added to primary MSNs that were co-cultured with midbrain neurons, it indeed increased the length and the number of dendritic branch points (Fig. 3). We identified MSNs based on DARPP-32 staining [9]. The number of spine-like protrusions from dendrites also increased in the MSNs that were treated with rasagiline. In addition, we examined the effect of rasagiline on dendritic structures of primary cultured MSNs without co-culturing midbrain neurons. We reasoned that the lack of co-cultured midbrain neurons would limit available monoamines and the effect of MAO-B inhibition would be limited if the observed dendritic restructuring is solely dependent on the increase in available monoamines. Rasagiline indeed failed to change dendritic length in this pure striatal culture. However, the number of branch points was decreased

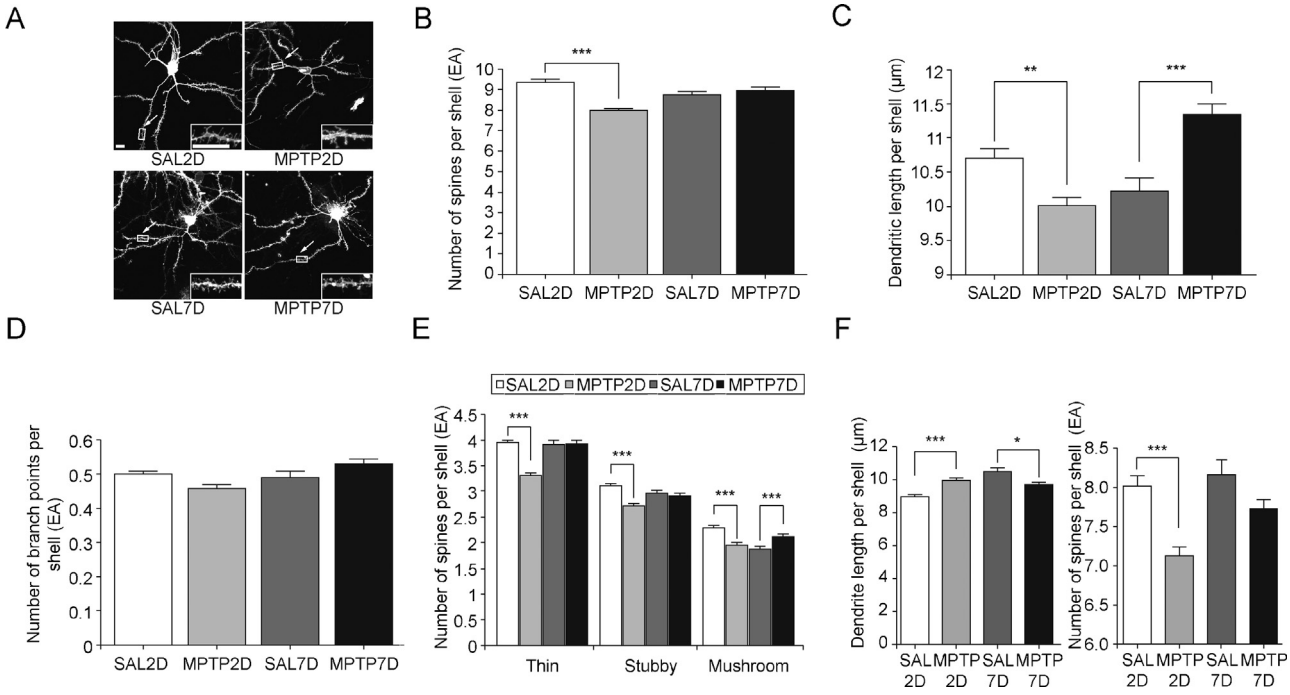

Fig. 2. The dendritic structures of striatal MSNs in the MPTP-lesioned mice are spontaneously restored. (A) Representative images of dendritic structure and spines from MPTP-lesioned mice and control mice. (B, C) The number of spines and dendritic length on MPTP2D were significantly decreased but restored by MPTP7D. (D) The number of branch points did not change significantly either in MPTP2D or MPTP7D. (E) Morphological analysis of spines showed that all subtypes significantly decreased in MPTP2D but were restored in MPTP7D. (F) The dendritic length and the number of spines (all subtypes combined) were reanalyzed from the striatal neurons after excluding cells in the dorsolateral quadrant.

All measurements of dendritic structures were made from the following: [(B–E), SAL2D, $n = 7691$ shells from 60 cells (6 mice); MPTP2D, $n = 5533$ shells from 43 cells (6 mice); SAL7D, $n = 3315$ shells from 25 cells (4 mice); MPTP7D, $n = 6143$ shells from 41 cells (4 mice); (F), SAL2D, $n = 2621$ shells from 19 cells (6 mice); MPTP2D, $n = 2866$ shells from 23 cells (5 mice); SAL7D, $n = 1455$ shells from 11 cells (4 mice); MPTP7D, $n = 3525$ shells from 24 cells (4 mice)]. The dorsolateral quadrant region of striatum was about ML 1.5–2.3 mm, DV −2.3 to −3.5 mm. Asterisks indicate different p-values ($^{**}p < 0.01$, $^{***}p < 0.001$). Scale bars indicate 10 μm.

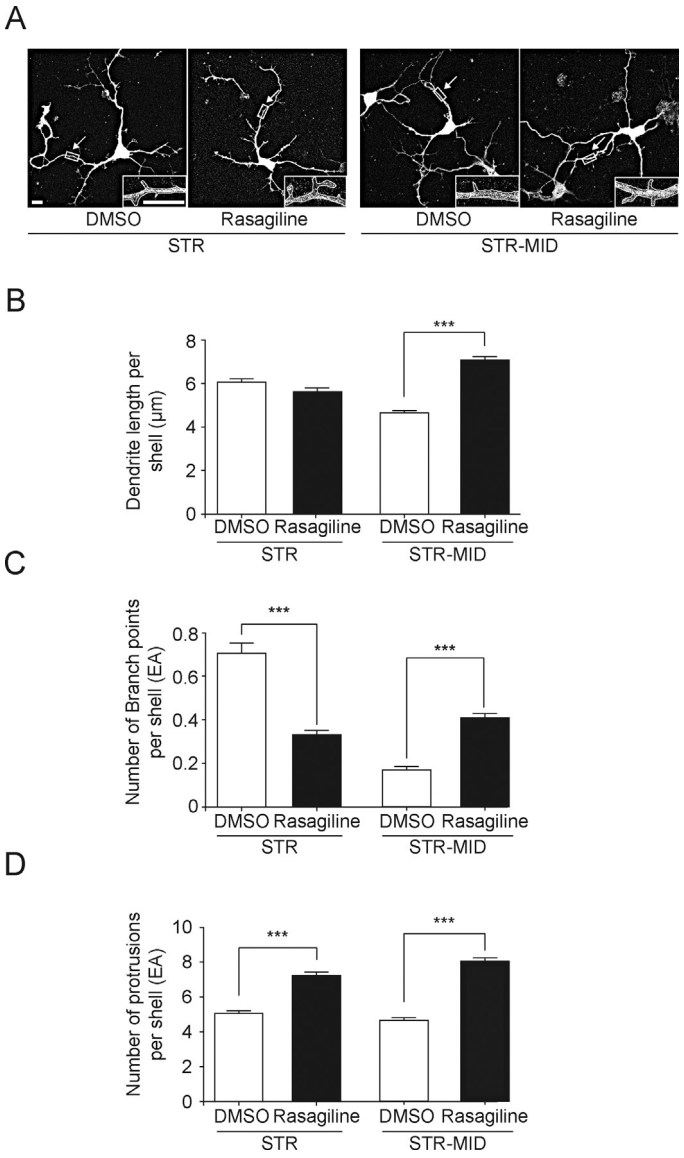

Fig. 3. Rasagiline remodels dendritic structure in cultured striatal. Left panels show images and data from dissociated neuronal cultures made of the striatum only (STR) and right panels show images and data from dissociated neuronal co-cultures made of the striatum and the midbrain tissues (STR-MID). (A) Representative images of cultured neurons and their dendrites are shown. (B) The length of dendrites per concentric shell is shown in graphs. (C) The number of dendritic branch points per concentric shell. (D) The number of spine-like, small protrusions was measured per concentric shell.
All measurements of dendritic structures were made from the following: STR culture: DMSO, $n = 1730$ shells from 11 cells, Rasagiline, $n = 935$ shells from 8 cells; STR-MID culture: DMSO, $n = 1004$ shells from 12 cells, Rasagiline, $n = 1651$ shells from 9 cells. Asterisks indicate a statistical significance ($^{***}p < 0.001$). Scale bars indicate 10 μm.

by rasagiline treatment in the striatum-only culture, which is completely opposite to what is observed in the striatum-midbrain co-culture system. Furthermore, spine-like protrusions were still increased in the absence of midbrain neurons.

4. Discussion

The dorsal striatum, major input structure of basal ganglia, receives and integrates inputs from various areas of the brain such as the cortex and the thalamus, conveying sensory, motivational, and movement information. The striatum then facilitates the control of behavioral actions that accomplishes desired outcome. In PD, typical motor symptoms of PD such as tremor, rigidity, and bradykinesia do not arise until the loss of DA neurons reaches a critical threshold, 70–80% loss of dopaminergic nerve terminals in the striatum and 50–60% loss of the SN perikarya [3]. This delay in the clinical onset of PD may be due to multifactorial compensatory mechanisms that occur at the several levels of the cortico-basal ganglia-thalamo-cortical loop [4]. In this study, we have shown that spontaneous recovery after acute MPTP administration is accompanied by the restoration of dendritic structures and spine density in MSNs. The loss of DA neurons and their terminals within the striatum was still extensive when behavioral recovery was apparent. It is, therefore, possible that the MSN's dendritic remodeling occurs as a compensatory response that keeps overall basal ganglia network activity within a normal range.

We have also shown that rasagiline administration could dramatically alter dendritic structures in cultured MSNs. Several studies have demonstrated that rasagiline possesses neuroprotective effects both *in vitro* and *in vivo* [5,16,18]. Our results suggest that the efficacy of rasagiline in PD might be, at least in part, a consequence of striatal dendritic remodeling. Some of the dendrite-remodeling effects may not be dependent on midbrain dopamine restoration because rasagiline could induce dendritic changes even without the source of dopamine in cultured MSNs. These are consistent with the results of our *in vivo* analysis. The length of dendrites was not increased in the region where DA denervation was severe, however, the number of spines was still recovered. These results are also somewhat consistent with previous findings that dopamine replacement alone cannot reverse the dendritic spine loss caused by dopamine depletion in PD. The levodopa treatment did not restore the dendritic spine density to control levels in rats with striatal dopamine denervation [8] and post-mortem studies of PD found that marked dendritic spine loss was still present although all patients had received levodopa or a dopamine agonist [19,21]. Our data imply that the striatal dendritic spines can be remodeled independently of the dopaminergic input, and MAO-B may have direct influence on MSN dendritic structure. MAO-B inhibitors are often used in combination with levodopa for the treatment of PD since it has been shown that a MAO-B inhibitor can improve the symptoms of PD in levodopa-treated patients and the animal model of PD [12,13]. Therefore, it may be that both functional dendritic remodeling of MSNs and DA replenishment are required for efficient reduction of PD symptoms.

5. Conclusions

In the present study, dynamic changes in the dendritic structure of striatal MSNs correlated with behavioral recovery in the mouse model of PD. Furthermore, rasagiline effectively increased the dendritic complexity of MSNs in culture. We propose that changes in the dendritic structure of striatal MSNs may serve a direct readout of motor-related symptoms and, therefore, restructuring of the dendrites of MSNs could be a target for effective therapeutic interventions in PD.

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