Protective effect of melatonin on 3-NP induced striatal interneuron injury in rats

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To confirm the effect of melatonin on 3-nitropropionic acid (3-NP)-induced striatal interneuron injury in rats, behavioral test, histology, immunohistochemistry and Western blotting were respectively used to characterize the behavioral changes of experimental animals in motor and cognition, the morphological changes of striatal interneurons and the expression level of protein markers induced by 3-NP. The results showed that (1) 3-NP induced dysfunction of experimental animals in movement, motor coordination and cognition could be relieved by melatonin treatment; (2) The 3-NP-induced lesion area was unvaryingly in dorsolateral striatum, with almost all neuronal loss in the lesion core, however, lots of neurons survived after melatonin treatment; (3) Immunohistochemical staining of the four interneuron types (parvalbuminergic, cholinergic, calretinergic, and neuropeptide Y-neuronal nitric oxide synthase co-containing) showed that, in the lesion core of 3-NP group, loss of the four interneuron types was obvious, but in transition zone, the processes and varicosities of calretinergic, and neuropeptide Y-neuronal nitric oxide synthase co-containing interneurons increased significantly. Melatonin treatment reduced the loss of the four interneuron types in the lesion core, and inhibited the increase of processes and varicosities in the transition zone; (4) Consistent with above results, the expression level of five interneuron protein markers were significantly increased in the striatum after melatonin treatment. Notably, in both the transition zone and the lesion core induced by 3-NP, TUNEL-positive cells were detected, but decreased significantly after melatonin treatment. The present results indicate that melatonin effectively protects the striatal neurons against the injury induced by 3-NP in rats.

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1. Introduction

Huntington’s disease (HD) is an inherited neurodegenerative disorder characterized by motor dysfunction, cognitive decline and emotional and psychiatric disorders (Folstein et al., 1986; Albin and Tagle, 1995). Morphological studies show that histopathological changes of HD involve striatal atrophy, which is mainly the result of a massive neuronal loss of the striatal medium spiny projection neurons, with the caudate nucleus being affected earlier and more severely than the putamen (Albin et al., 1989; Heizmann and Braun, 1995; Vonsattel et al., 1985; Hedreen and Folstein, 1995; Cipriani et al., 2008). Several types of interneurons appear to be relatively spared in HD, namely the GABAergic aspiny interneuron type that co-contain the neuropeptides somatostatin (SS), neuropeptide Y (NPY), the enzyme nicotinamide adenine dinucleotide phosphate diaphorase (NADPHd) or nitric oxide synthase (NOS) (Dawbarn et al., 1985; Ferrante et al., 1987; Kowall et al., 1987), and the large cholinergic aspiny interneurons (Kowall et al., 1987; Ferrante et al., 1987), whereas striatal projection neurons are most severely affected in HD (Deng et al., 2004; Ferrer et al., 1994; Vonsattel and DiFiglia, 1998). It suggests that different striatal neuron types showed selectively vulnerability during the course of HD.

To understand HD pathogenic mechanisms, several animal models involving different injury mechanisms (such as QA, 3-NP and transgenic model) have been used to study HD. These models simultaneously induce motor deficits and striatal pathological changes similar to HD. In QA and 3-NP models, a clear demarcation of the site of striatal damage is visible, with a lesion core of extensive destruction surrounded by the transition zone with lesser damage (Huang et al., 1995; Figueredo-Cardenas et al., 1997). A similar region of lesser neuronal loss called the penumbra also surrounds the site of severe damage in ischemic cerebral damage. Enhancing neuronal survival in the penumbra has been proposed to be a therapeutic goal for central nervous system injury (Wang et al., 2000; Liu et al., 2010).

Melatonin (N-acetyl-5-methoxytryptamine), is a neurohormone synthesized in the pineal gland. It functions in many physiological processes, such as photoperiod information, reproduction, immune response, and aging process (Martin et al., 2000). Recently, melatonin is found to possess free radical scavenging and antioxidant...
properties (Reiter et al., 2001). Furthermore, the efficacy of melatonin in reducing the toxicity of some mitochondrial poisons (such as rotenone, 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine, 3-nitropropionic acid and cyanide) is examined, which confirms the protective effect of melatonin against mitochondrial injury (Saravanan et al., 2007; Chen et al., 2005; Nama et al., 2005; Yamamoto and Mohanan, 2002).

The present study sought to better characterize the response of striatal four major interneuron types, which containing parvalbumin (Parv), calretinin (Cr), choline acetyltransferase (ChAT), and co-containing neuropeptide Y (NPY) and neuronal nitric oxide synthase (nNOS), to 3-NP-injured injury, as well as the protective effect of melatonin on functional disorder of motor and cognition and striatal neuronal injury induced by 3-NP in rats. The detected regions mainly focused on the lesion core and transition zone of striatum.

2. Material and methods

2.1. Animal model of 3-NP and melatonin treatment

Thirty adult male Sprague–Dawley rats (250–300 g, obtained from the Center of Animal Experiments of Sun Yat-sen University) were used. All procedures were in strict accordance with protocols approved by the China institutional ethics committee, and all efforts were made to reduce the number of animals used. Animals were housed in an air-conditioned room under an even light–dark cycle, with food and water ad libitum. The animals were randomly divided into three groups. The 3-NP group (10 rats) received 3-NP (dissolved in saline to a concentration of 15 mg/ml, pH 7.4, Sigma) intraperitoneally twice a day for 5 days at a dose of 25 mg/kg/day. The melatonin group (10 rats) received both 3-NP and melatonin
for 5 days. Melatonin (dissolved in 5% ethanol/saline, Sigma, i.p.) was delivered at a dose of 10 mg/kg/day, 30 min prior to 3-NP administration. The control group (10 rats) was matched by weight and received only vehicle. Rats were evaluated daily for motor and cognitive deficits during the two administrations, beginning with the first injection. The animals were sacrificed one day after the last injection. Five animals per group were used for histology and immunohistochemistry, and the rests were used for Western blotting.

2.2. Behavioral testing

2.2.1. Balance beam

The rats were tested three times a day for the 5 injection days on the balance-beam task according to Shear et al. (1998). The animals were trained to travel from the suspended end of a narrow beam (120 cm length, 7 cm width, elevated 100 cm above a thick foam cushion, Fig. 1A and A’)) into a goal box (24.5 × 20 × 18 cm). The latency to initiate movement and time of trial completion were recorded by two observers. Latency to initiate movement consisted of the time interval between the moment the animal was placed on the beam and the time the animal left the starting position and stepped over a preset mark, drawn 20 cm away from the suspended end of the beam. Animals were given 3 min to complete the task before being removed from the beam. If the animal fell, or took more than 3 min, the task was recorded as incomplete.

2.2.2. Grip strength

Grip strength (Shear et al., 1998) was measured by recording the length of time that the rat was able to hold onto a steel wire (2 mm in circumference; 35 cm in length, Fig. 1B and B’) suspended 50 cm above a thick foam cushion. Grip strength was measured three times per day for the five consecutive injection days.

2.2.3. Morris water maze task

In the Morris water maze task (Vorhees and Williams, 2006), the rats were trained for 5 consecutive days. The rats were let down in four random places (N, S, E, W) in the pool. The order of these was changed daily in a random manner. The rats were trained four times a day (2 min/trial or until they found the platform). After the 2 min swim, they were allowed to stay on the platform for 30 s before the next swim trial. The tracking was recorded using video camera and Ethovision software (Noldus, Holland). Owing to different swim speeds in the different groups, the latencies of training days 1–5 were compared with the average latency for each day.

2.3. Histocemistry and immunohistochemistry

Animals were anesthetized with chloral hydrate 350 mg/kg and perfused first with 300 ml of 0.9% sodium chloride and then 400 ml of 4% paraformaldehyde (in 0.1 M phosphate buffer, pH 7.4). Brains were then removed and postfixed in the same fixative, and then coronal sections (30 μm) were cut on a vibratome (VIBRATOME, #053746). Some sections were stained with HE (hematoxylin and eosin, HE), and Nissl-stained according to conventional staining methods (Voogd and Feirabend, 1981).

Sections were pretreated with 0.3% H2O2 in 0.01 M PBS at 37°C for 30 min. To carry out conventional single-label immunohistochemistry, separate series of sections were incubated for 48 h at 4°C in mouse anti-Parv (1:1000, Sigma), rabbit anti-ChAT (1:1000, Millipore), rabbit anti-nNOS (1:800, Santa Cruz Biotechnology), rabbit anti-CR (1:2000, Millipore), and rabbit anti-NPY (1:5000, ABCAM). Sections were then rinsed and incubated in anti-mouse IgG or anti-rabbit IgG (1:200, Sigma), followed by incubating in the appropriate mouse or rabbit PAP complex (1:200, Sigma) at room temperature for 2 h. The DAB-peroxidase reaction (0.05% in 0.01 M PBS, pH 7.4, Sigma) was carried out for 2–8 min and mounted onto gelatin-coated slides, dried, dehydrated, cleared with xylene, and covered with neutral balsam.

To determine if striatal neurons were undergoing apoptosis following 3-NP treatment, TUNEL assay was combined with immunofluorescent detection. For these studies, sections were incubated in primary antibody for mouse anti-NeuN (1:500, Millipore), and the sections were subsequently incubated for 2 h at room temperature in rhodamine-conjugated goat anti-mouse IgG (1:200, Jackson ImmunoResearch). All sections were thereafter rinsed three times in 0.01 M PBS, and TUNEL-stained (In Situ Cell Death Detection Kit, POD, Roche) according to the manufacturer’s instructions. Then the sections were mounted on gelatin-coated slides, and coverslipped with glycerol. Sections were viewed and images captured using a fluorescence microscope.

2.4. Western blotting

Western blotting was carried out for the marker proteins for each type of interneuron examined. Rats were decapitated after being anesthetized with chloral hydrate, and the striatum was extracted and homogenized in a freshly prepared lysis buffer with protease inhibitors. The homogenate was centrifuged at 1500g for 25 min, and protein concentration determined using BioRad DC protein assay (BioRad, Laboratories). Samples were separated by sodium dodecyl sulfate-polyacrylamide gel electrophoresis (1% SDS–PAGE), and transferred to PVDF membranes (Millipore). Membranes were incubated in blocking buffer (5% skim milk in TBST), then with mouse anti-Parv (1:1000, Sigma), rabbit anti-ChAT (1:1500, Millipore), rabbit anti-nNOS (1:1500, Santa Cruz Biotechnology), rabbit anti-CR (1:8000, Millipore), rabbit anti-NPY (1:5000, ABCAM), or rabbit anti-β-actin (1:2000, Millipore) in TBST overnight at 4°C. Incubated membranes were then treated with secondary antibody conjugated with horseradish peroxidase in TBST for 2 h at 37°C. Blots were developed by enhanced

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**Fig. 2.** The location of the lesion core and transition zone in injured striatum. Images A–C show the location of the lesion core (‘’) and transition zone (‘•’) in 3-NP-injured striatum. Image A shows Nissl staining, and images B and C show immunolabeling for NeuN and ChAT, respectively.
chemiluminescence, and digitally scanned. The optical density of each resulting labeled band was measured using an image analysis program.

2.5. Data collection and statistical analysis

In each group, eight sections for each rat were analyzed per neuron type. Quantitative analysis of the four types of striatal interneuron was performed on adjacent coronal sections of the striatum. The sections were taken from levels corresponding approximately to the interaural plane from 10.70 to 8.74 mm (according to the atlas of Paxinos and Watson, 1986). For each level, adjacent sections were stained for HE, Nissl, and immunostained for NPY, nNOS, ChAT, PV, and Cr. For HE and Nissl, the number of labeled perikarya counted in five randomly selected areas (0.01 mm² for each) in each zone (core, transition, peripheral) for each section; for the interneuron types, the total number of labeled perikarya counted in each zone for each section. The location of three zones in 3-NP animals was based on Fig. 2. To measure the density of axons and the number of varicosities of the four types of interneuron, five areas were randomly selected in each zone, and the number of intersecting processes along a 100 μm length was counted as the density of processes, while varicosity abundance was presented per 100 μm axon length. All data in this study are presented as means ± SD. The statistical significance of the results was evaluated by One-Way ANOVA with multiple comparison t-tests with SPSS analytical software and P < 0.05 was considered as significant.

3. Results

3.1. Protective effect of melatonin on the behavioral changes induced by 3-NP

3.1.1. Assessments of motor deficit

On the balance-beam task, it took longer time for 3-NP-treated rats to initiate movement (18.96 ± 3.5) than controls (3.04 ± 0.6,
$F = 56.27, P < 0.05$). All control rats were able to complete the task, whereas most of the 3-NP treated rats had a difficult time in moving across the narrow beam and several froze into a rigid posture and failed to move past the beam ($F_{1, 3} = 13.0$, $P < 0.05$). Statistically, the 3-NP rats took more time to cross the entire beam ($48.78 \pm 9.2$, $F = 34.61, P < 0.05$). After melatonin treatment, the rats took less time to initiate movement ($10.2 \pm 1.0$) and cross the entire beam ($32.4 \pm 3.1$) than the 3-NP rats ($F = 23.74$ and $14.23, P < 0.05$).

The rigidity of the 3-NP treated rats was also confirmed by the grip-strength task (Shear et al., 1998), which displayed a progressive rigidity that tended to increase over time, as evidenced by the extended hang times observed at different times post-surgery. During the grip-strength task, 3-NP treated rats resulted in a profound increase in hang times ($15.6 \pm 3.1$) compared to controls ($8.9 \pm 2.0, F = 69.20, P < 0.05$). After melatonin treatment, the rats took less time to initiate movement ($10.2 \pm 1.0$ and cross the entire beam ($32.4 \pm 3.1$) than the 3-NP rats ($F = 23.74$ and $14.23, P < 0.05$).

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### 3.2. Melatonin protects striatum against injury induced by 3-NP

To evaluate the protective effect of melatonin on the striatal lesion induced by 3-NP, histological method was used. In all the 3-NP-treated rats, a clear lesion was located in the dorsolateral striatum bilaterally (Fig. 3B and E). In striatal lesion area, neuronal loss was observed in the lesion core. Statistical analysis showed a significant reduction in numbers of neurons in the lesion core in 3-NP group ($54.0 \pm 2.0$) compared with controls ($7.0 \pm 0.4, F = 18.12, P < 0.05$). HE and Nissl stains also showed that the lesion core was surrounded by a narrow annulus transition zone with lesser neuronal loss (Huang et al., 1995). A few large neurons were observed in this zone, mixed with some medium-sized neurons (Fig. 3B and E). In the region outside the transition zone (termed the peripheral zone, Huang et al., 1995), cells were indistinguishable from normal in number and appearance. The transition zone could be distinguished from both the lesion core and the peripheral zone because it was paler in HE and Nissl staining, due to the absence of the necrosis seen in the lesion core and the neuron abundance in the periphery (Fig. 2). Statistical analysis also revealed that after 3-NP treatment, the neuronal number decrease in transition zone ($36.1 \pm 1.9$) in comparison with the controls ($53.0 \pm 3.1, F = 25.34$).
P < 0.05, Fig. 4A). However, in melatonin-treated rats, the necrosis diminished obviously in the lesion core with lots of cells survived, and the transition zone could not be distinguished from both the lesion core and the peripheral zone (Fig. 3C and F). In both the lesion core and transition zone, melatonin-treated rats resulted in a profound increase in neuronal number compared to 3-NP rats \((F = 89.12\) and \(72.12, P < 0.05\), Figs. 3C, F, 4A).

3.3. Reaction of striatal interneurons and their protein markers to 3-NP and the protective effect of melatonin

3.3.1. Morphological changes in striatal interneurons

To characterize changes in the four interneuron types induced by 3-NP and the protective effect of melatonin, each type was immunolabeled using a unique marker for it, with two markers used for the nNOS/NPY/SS neurons. In 3-NP rats, there was a nearly complete loss of all four interneuron types in the lesion core \((F = 23.50, 8.12, 12.14 \) and \(14.34, P < 0.05\), Fig. 4B). By contrast, in the peripheral zone, interneurons were normal in number compared to those in the controls (Fig. 4D). A significant increase was observed in the transition zone for NPY+/nNOS+ and Cr+ interneurons in terms of an increased number of processes and varicosities \((F_{(NPY)} = 34.56 \) and \(23.12, F_{(nNOS)} = 45.67 \) and \(89.34, F_{(Cr)} = 13.47, P < 0.05\), Figs. 4E, F, 5B, E, and 8B). There was also a trend in the transition zone for process reduction of Parv+ neurons \((F = 10.09, P < 0.05\), Fig. 4E, Fig. 6B). Some ovoid hypochromatic vacuoles were visible in ChAT+ axons (Fig. 7B). However, in melatonin-treated rats, there were more interneurons survived in the lesion core compared with the 3-NP rats \((F = 23.12, 9.23, 33.45, 12.67, 67.45 \) and \(56.10, P < 0.05\), Fig. 4B). In addition, statistical analysis showed a significant reduction of processes and varicosities for NPY+/nNOS+ and Cr+ interneurons in the transition zone after melatonin treatment \((F_{(NPY)} = 14.50 \) and \(53.13, P < 0.05\), Fig. 5.)

![Image](Image_url)

**Fig. 5.** Reaction of striatal NPY+/nNOS+ interneurons in 3-NP and 3-NP+MT rats. A, A’ and D, D’ show NPY+/nNOS+ interneurons in control, from which the distribution pattern and morphology of this interneuron type is evident. Images B, B’ and E, E’ show the quantitative and morphological changes in NPY+/nNOS+ interneurons in 3-NP rats, with most of the neurons lost in lesion core (*) and the density of processes and beaded axons significantly increased in the transition zone (*). Images C, C’ and F, F’ show NPY+/nNOS+ interneurons in 3-NP+MT rats, which show the reduction of the neuronal lose in lesion core, and the reduction of processes and varicosities in transition zone in 3-NP+MT rats. Images A–F were the same magnification; Images A’–F’ were the same magnification.
$F_{(nNOS)} = 47.23$ and $29.68$, $F_{(Cr)} = 23.58$, $P < 0.05$, Figs. 4E, F, 5C, and the reduction of Parv+ neuron processes induced by 3-NP diminished in melatonin rats (Fig. 6C). The statistical analysis showed a significant difference ($F = 15.35$, $P < 0.05$, Fig. 4E).

### 3.3.2. Changes of protein markers in striatal interneurons

Western blotting revealed that treatment with 3-NP significantly decreased NPY, nNOS, Parv, ChAT and Cr protein in rat striatum (Fig. 9). However, in melatonin group, decrease of these proteins in striatum was less than 3-NP rats ($F = 8.34$, 10.90, 23.80, 34.28 and 18.76, $P < 0.05$, Fig. 9).

### 3.4. Melatonin reduced striatal apoptosis induced by 3-NP

In control rats, no TUNEL labeling was observed in striatum, but after 3-NP administration, TUNEL positive profiles were detected in striatum (Fig. 10A), which were mainly found in the transition zone, but some could also be seen scattered in the lesion core. After melatonin treatment, TUNEL labeling decreased significantly compared with 3-NP group in both lesion core and transition zone (Fig. 4G, Fig. 10A'). The TUNEL labeling was mainly in nuclei that also showed a typical pattern of programmed cell death, such as fragment and pyknosis. Double-labeling for TUNEL and NeuN, as shown in Fig. 10B', revealed that in transition zone, 21.2 ± 3.8% positive neurons were labeled for TUNEL, and in lesion core, 8.5 ± 0.6% (Fig. 4H). Statistical analysis also showed that the percentage of positive neurons labeled for TUNEL decrease in melatonin group, compared to the 3-NP group ($F = 47.12$, $P < 0.05$, Fig. 4H, Fig. 10C').

## 4. Discussion

### 4.1. Functional characteristics of striatum and its selective damage induced by 3-NP

Some specific types of toxins, including kainic acid, ibotenic acid, and quisqualic acid, have been used to study HD pathogenesis (Beal et al., 1993; Coyle and Schwarcz, 1976; Ferrante et al., 1993; Hantraye et al., 1990; McGeer and McGeer, 1976; Schwarcz et al., 1983). 3-NP was introduced as an HD model because its behavioral and neuropathological features are similar to those seen in HD (Beal et al., 1993; Ludolph et al., 1991; Wullner et al., 1994; Reiner et al., 1988). Further studies documented that systemic administration of 3-NP might better model HD than intracerebral microinjection (Du et al., 1996; Miller and Zaborszky, 1997; Deng et al., 2004). As model of HD, our data are in agreement with several other studies, since our 3-NP injections caused motor impairments on balance-beam and grip-strength, as well as cognitive impairments in the Morris water maze. Since 3-NP unvaryingly induced marked a lesion in the dorsolateral striatum, it seems the cognitive and behavioral symptoms stem from the interruption of specific circuits devoted to these functions in dorsolateral striatum.

### 4.2. Reaction of striatal interneurons in the transition zone to 3-NP-induced injury

The pathological hallmark of HD is a massive reduction of the striatal volume (Vonsattel et al., 1985), which is the result of loss of spiny projection neurons, while the interneurons are relatively...
Interneuron loss in the lesion core produced by 3-NP, however, is comparable to projection neuron loss. For example, there was a comparable loss of spiny neurons stained for calbindin and medium-sized aspiny neurons containing somatostatin, NADPH-diaphorase and NPY in the 3-NP lesion core (Beal et al., 1993). In the present study, both immunohistochemistry and Western blotting were used to observe the changes in the four striatal interneuron types induced by 3-NP. The results revealed that all types of interneuron were extensively lost in the lesion core, and their protein levels decreased after the treatment of 3-NP. More noteworthy was the normal survival we observed of the interneuron types in the transition zone, in which projection neuron loss was still high. Thus, striatal interneurons did show relatively greater resistance to 3-NP toxicity than did striatal projection neurons. The survival of the Cr+ and NPY+/nNOS+ interneurons in the transition zone was accompanied by an increase in labeling of their processes and varicosities (Sun et al., 2002; Massouh et al., 2008). The significance of this phenomenon is uncertain, and it is unclear if this is a protective response or a response to projection neuron loss (e.g. is projection neurons inhibit these two interneuron types). Because Cr plays an important role in the maintenance of intracellular calcium homeostasis, its presence in some neurons may protect them against the massive entry of calcium that may result from NMDA receptor overstimulation. Another possibility is that interneurons show regenerative changes and create new inputs to replace lost connections. The noteworthy possibility is that the hyperplasia of the axons of the interneurons involves regenerative phenomena similar to those previously reported for neostriatal spiny neurons in HD (Graveland et al., 1985; Her and Goldstein, 2008; Perlson et al., 2010).

4.3. Protective effect of melatonin on 3-NP induced injury

Melatonin is a potent scavenger of free radicals, and regulates the activity and expression of antioxidant enzymes (Martin et al., 2000). Previous studies have shown that melatonin protects the brain against a series of injuries produced by agents or neurological insults such as 6-hydroxydopamine (Borah and Mohanakumar, 2009), kainic acid (Tan et al., 1998), and stroke (Joo and Manev, 1998). Among the protective effects of melatonin in excitotoxicity in experimental models of HD, the ability of melatonin against quinolinic-acid-induced oxidative damage in rat brain has been widely investigated (Cabrera et al., 2000). In addition, Tunez et al. (2004) reported that melatonin could prevent the reduction in succinate dehydrogenase activity in response to 3-NP. Nama et al. (2005) also revealed that melatonin given before and after the 3-NP injection attenuated striatal neuronal loss, limited the degree of asymmetric rotational movement, preserved dopamine levels and reduced the amount of lipid and protein oxidation. While only several studies have been published related to the use of melatonin to ameliorate 3-NP toxicity, and the reports showed conclusively that melatonin effectively counteracts the neuronal damage associated with succinate dehydrogenase poisoning (Reiter et al., 2008). In the present study, behavioral testing, histology, immunohistochemistry and Western blotting were used to investigate the potential neuroprotective role of melatonin in 3-NP induced injury. The present results revealed that the disorder of motor and
cognition induced by 3-NP was prevented by melatonin, and striatal necrosis and interneuronal damage were significantly attenuated by melatonin treatment. These results demonstrated that melatonin effectively decreased the 3-NP-induced
dysmetabolism and protected against the 3-NP-induced striatal injury, which suggest the possibility for clinical applications of melatonin in neuroprotective drugs for neurodegenerative disease such as HD.

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