Depressive-like behavior in mice recently recovered from motor disorders after 3-nitropropionic acid intoxication

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Abstract: Objective Striatum may be involved in depressive disorders according to the neuroimaging analysis and clinical data. However, no animal model at present supported the possible role of striatum in the pathogenesis of depression. In the present study, we have investigated the depressive-like behavior in mice recently intoxicated with 3-nitropropionic acid (3-NP), a widely known toxin that selectively damages the striatum in the brain. **Methods** Mouse model was made with subacute systemic 3-NP treatment, and the depressive-like behavior was measured using the duration of immobility during forced swimming test (FST). **Results** When the mice at day 15 post-intoxication just totally recovered from motor deficits, the duration of immobility in FST was significantly longer than that in controls. The depressive-like behavior was not due to the fatigue or general sickness following 3-NP intoxication and could be reversed by the antidepressant, desipramine hydrochloride. In two successive FST in 24 h interval, the depressive-like behavior could be observed again in subsequent FST (at day 16 post-intoxication), and the mice presented a normal “learned helplessness”. **Conclusion** A novel depression animal model could be established in mice during the initial period of recovery from 3-NP intoxication. The depression-like behavior might occur independently without involvement of cognitive defects, and the striatal lesions may underlie the depression-like behavior attributable to 3-NP intoxication.

Keywords: 3-nitropropionic acid; forced swimming test; depression; striatum; mice

1 Introduction

Depression is a heterogeneous disorder with a highly variable course and an inconsistent response to treatment^[1,2]. Although the pathophysiology of depression has not been established, some brain regions, such as hippocampus, amygdala, prefrontal cortex, and striatum, are considered having played important roles^[3-7].

The striatum that forms a great part of fronto-subcortical circuits may be involved in emotion recognition and emotional responses according to the neuroimaging analysis and neuropsychological studies^[8-10]. A series of clinical data has indicated a connection between depression and the disorders of striatum^[6,10].

The prevalence of depression is 30% for all patients of Huntington's disease (HD)^[10,11], higher than the rates of depression in persons with other equally disabling disorders. There are strong clinical evidence, in HD patients, that the abnormality of striatum precedes the obvious motor disturbance and psychiatric manifestations, e.g., depression may predate motor signs by a decade^[12-17]. Both striatum change and depression occur early in HD, hence some authors believe that at least a proportion of HD patients suffer symptoms of depression secondary to the neuropathological changes in the basal ganglia, other than to the increased distress of motor deficits and anticipation of pending events^[13,14,17]. Recently, deep brain stimulation of the ventral caudate nucleus has proved effective in the treatment of obsessive-compulsive disorder and major depression^[18]. Besides these clinical data, however, currently, there is no animal model or study that supports the possible role of striatum in the pathogenesis of depression.

3-Nitropropionic acid (3-NP), a widely known plant-borne

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Article ID: 1673-7067(2008)04-0225-06
CLC number: Q427
Document code: A
Received date: 2008-03-04

and fungal toxin and an irreversible inhibitor of succinate dehydrogenase of the mitochondrial complex II, induces selective damage to the striatum in humans and animals, and produces HD-like clinical features^[19-22]. Fernagut *et al.* found that subacute systemic administration of 3-NP in mice induced a distinct motor disorder, but most of affected mice strikingly recovered from this motor disorder within 7-10 d^[20]. Forced swimming test (FST) is one of the mostly-used animal models for screening antidepressants and analyzing depression-like behavior in genetically modified mice^[23-26]. Based upon these previous studies^[23-25], we observed the duration of immobility of mice in FST and investigated the depressive-like behavior in mice that just totally recovered from motor deficits after 3-NP intoxication.

2 Materials and methods

2.1 Animals and reagents Male mice of Kunming strain (Laboratory Animal Centre, Tongji University, Shanghai, China), aged 10 weeks, were used in the experiments. The mice were housed in an animal room with room temperature (23±2) °C, relative humidity (55±10)%, a 12-h alternating light-dark schedule and free access to food pellets and tap water. The mice were allowed at least one week to adapt to the laboratory environment before any behavioral assessment. All studies were carried out in accordance with the guideline of the China Council on Animal Care. All efforts were made to minimize animal suffering and reduce the number of animals used.

3-NP and an antidepressant, desipramine hydrochloride (DMI), that both of them are analytical grade and purchased from Sigma-Aldrich in USA, were dissolved in normal saline to concentration of 8 mg/mL and 10 mg/mL, respectively.

2.2 FST The procedure of FST was adopted as described by Porsolt *et al.*^[26] with minor modification. Briefly, the mice were individually placed in a glass cylinder (30 cm in height, 20 cm in diameter) filled with 20-cm high of water (23-25 °C), and forced to swim for 6 min in the routine FST^[26], or 4 min in the modified FST-1 and FST-2. The durations of immobility were observed and documented during the final 2-min (in the modified FST-1) or 4-min (in the routine FST) interval, or for the whole 4 min (in the modified FST-2) of the test. All test swim sessions were recorded by a video camera positioned directly above the cylinder. Immobility period was regarded as the time spent by a mouse floating in the water without struggling/swimming and making only those movements

necessary to keep its head above the water.

2.3 Rotarod The procedure of the Rotarod was based on published studies with some modifications^[20,27]. Mice were placed on a stationary rod (diameter = 70 mm) and trained to stay on it as the rod rotated at 5 r/min. Usually 4 to 6 training sessions on consecutive days (each was constituted by a maximum of 10 trails) were needed to achieve the maximal performance, which took 180 s. At the end of training period, each mouse reached the skill level of 180 s on its first run. Mice were retested once daily during 3-NP intoxication process, once every other day in day 6 to day 15, and once every two weeks in day 16 to day 45 post-intoxication. The mean time at which the mouse fell off the rotating rod for consecutive three trials was used as the assessment criterion of competency on this skill test.

2.4 Experiment design and treatment A series of three separate experiments was conducted in this study. In the first set of experiments, the routine FST was adopted. The mice, just totally recovered from 3-NP intoxication, were forced to swim for 6 min and were observed for the duration of immobility in the final 4 min period of tests. In this set of experiments, twenty-one mice were divided into two groups, 3-NP group 1 (3-NP1) and control group 1 (Ctrl). Each mouse in 3-NP1 ($n = 14$) received two separated 3-NP i.p. injections daily, 12 h apart with following schedule: 20 mg/kg × 4, 40 mg/kg × 6 (total cumulated dose 320 mg/kg in 5 d). This intoxication paradigm was modified from the study of Fernagut *et al.*, and would induce striatal lesions and a distinctive motor disorder in C57Bl/6 male mice aged 16-20 weeks^[20]. Each mouse in Ctrl ($n = 7$) received i.p. vehicle injections with the same volume and time schedule as 3-NP1. Routine FST was performed in day 15 and day 45 post-3-NP-intoxication.

In the second set of experiments, modified FST-1 protocol was adopted. The mice were forced to swim only for 4 min, the depressive-like behavior was judged according to the durations of immobility in the final 2 min, which was shorter 2 min than that in the routine FST. If the depressive-like behavior observed in previous routine FST did not be confirmed in this condition, the depressive-like symptom could be attributed to the fatigue/general sickness which mice might still suffer for recent 3-NP intoxication, although these mice did not present any motor disorders at day 15 post-intoxication. We also investigated the effect of DMI on the depressive-like state in the modified FST-1. Fifty-one mice

were divided into four groups, 3-NP group 2 (3-NP2), 3-NP group 3 (3-NP3), control group 2 (Ctr2) and control group 3 (Ctr3). The mice in 3-NP2 ($n = 16$) and 3-NP3 ($n = 16$) received 3-NP injections and the intoxication paradigm was the same as described for 3-NP1. Ctr2 ($n = 9$) and Ctr3 ($n = 10$) received vehicle injections with the same volume and time schedule as those in 3-NP2 and 3-NP3. Modified FST-1 was performed at day 15 post-intoxication. The mice in 3-NP3 and Ctr3 were furnished with DMI i.p. injection 30 min prior to the modified FST-1, at dosage of 10 mg/kg^[23].

In the third set of experiments, we performed modified FST-2 to investigate whether the possible cognitive defects induced by 3-NP intoxication contribute to the depressive-like behavior. Mice were forced to swim for 4 min twice in a 24-h period, in which we observed the duration of immobility for the whole 4 min of test. In this set of experiments, eighteen mice were divided into two groups, 3-NP group 4 (3-NP4) and control group 4 (Ctr4). Mice in 3-NP4 ($n = 11$) received 3-NP via i.p. with the paradigm same as aforementioned for 3-NP1. Mice in Ctr4 ($n = 7$) received vehicle injections with the same volume and time schedule as those in 3-NP4.

2.5 Statistical analysis All data were expressed as mean $\pm$ SEM and analyzed using the SPSS statistical software package (version 13.0). Variance (ANOVA) was used to analyze the differences between different groups. $P < 0.05$ was considered to be statistically significant.

3 Results

3.1 The first set of experiments In 3-NP1, two mice died at

day 7 and day 10 post-intoxication, respectively. All of 12 mice developed motor disorders at day 6 post-intoxication, with symptoms ranging from slight motor slowing, transient hindlimb dystonia to permanent hindlimb dystonia, kyphosis, hindlimb claspings, and global postural adjustment impairment. Rotarod test was markedly disrupted at day 6, as demonstrated by significant deficit compared to the control and baseline performances (Table 1). By day 15 post-intoxication, although two mice still had some slight to moderate motor disorders, all other 10 mice recovered entirely from the motor disorders at this point and presented normal gait. No difference was detected in performances on the Rotarod test between 3-NP1 and Ctr1 or baseline (Table 1), and their weight was no difference compared to the control either (Table 1). The 10 mice appeared healthy again, and were used for the further FST experiments. Figure 1 shows the duration of immobility in the routine FST in mice recovered from 3-NP intoxication. The mice in 3-NP1 at day 15 post-intoxication displayed a significant longer length of immobility, compared to those in Ctr1 [$F(1,15) = 4.819, P = 0.044$], while there was no difference between 3-NP1 and Ctr1 at day 45 post-intoxication [$F(1,15) = 1.188, P = 0.293$].

3.2 The second set of experiments In 3-NP2, two mice died at day 4 and day 5 post-intoxication, respectively, and one failed to recover at day 15. The residual 13 mice that displayed motor impairment at day 6, similar to those observed in 3-NP1, recovered by day 15 (Table 1) and entered further experiments. In 3-NP3, one mouse died at day 4 and three mice failed to recover at day 15, the remaining 12 mice entirely

Table 1 The performance of mice in the Rotarod test and the mouse weight prior to and post 3-NP-intoxication

Groups	Rotarod mean time (s)			Weight (g)	
	Baseline	Day 6	Day 15	Baseline	Day 15
Ctr 1 ($n = 7$)	163.5 $\pm$ 15.2	171.7 $\pm$ 14.3	178.6 $\pm$ 2.4	43.0 $\pm$ 2.1	44.7 $\pm$ 2.5
3-NP1 ($n = 10$)	163.1 $\pm$ 17.0	43.7 $\pm$ 21.9**	175.2 $\pm$ 7.0	41.4 $\pm$ 1.8	43.9 $\pm$ 1.3
Ctr 2 ($n = 9$)	163.5 $\pm$ 25.7	173.4 $\pm$ 11.7	173.1 $\pm$ 10.7	—	—
3-NP2 ($n = 13$)	160.2 $\pm$ 27.4	31.6 $\pm$ 26.1**	174.9 $\pm$ 6.5	—	—
Ctr 3 ($n = 10$)	165.2 $\pm$ 23.8	171.9 $\pm$ 11.7	166.7 $\pm$ 19.1	—	—
3-NP3 ($n = 12$)	168.2 $\pm$ 19.2	35.3 $\pm$ 25.6**	168.5 $\pm$ 16.6	—	—
Ctr 4 ($n = 7$)	165.9 $\pm$ 15.3	179.6 $\pm$ 0.7	179.0 $\pm$ 1.7	—	—
3-NP4 ($n = 10$)	167.4 $\pm$ 12.3	85.6 $\pm$ 30.1**	175.2 $\pm$ 7.7	—	—

Data were collected from 3-NP-intoxicated mice that restored entirely from motor deficits at day 15 post-intoxication. Rotarod tests in 3-NP-intoxicated mice in 3-NP1, 3-NP2, 3-NP3, and 3-NP4 were performed at baseline, then at day 6 and day 15 post-intoxication, compared to vehicle-injected mice in Ctr1, Ctr2, Ctr3 and Ctr4, respectively. Weights of mice in 3-NP1, compared to weights of mice in Ctr1, were determined at baseline, then at day 15 post-intoxication. ** $P < 0.01$.

recovered (Table 1) and were used for further experiments. Figure 2 shows the duration of immobility in the modified FST-1 in mice recovered from 3-NP intoxication and the effect of DMI. The mice at day 15 post-intoxication, just recovered from motor disorders caused by 3-NP intoxication, yet again demonstrated a longer duration of immobility. Although the mice were forced to swim less 2 min in modified FST-1 (compared to routine FST), there was much more significant difference between mice in 3-NP2 and those in Ctr2 [$F(1,20) = 8.542$, $P = 0.008$]. Therefore, the fatigue factor is at least not the main cause for the prolongation of immobility in mice with 3-NP treatment. The DMI at dosage of 10 mg/kg abolished the difference between 3-NP3 and Ctr3, and shortened the duration of immobility no matter whether the mice were treated with 3-NP. The duration of immobility for the mice

Fig. 1 The first set of experiments showing the duration of immobility of mice in routine FST at day 15 and day 45 after 3-NP intoxication. Slight black and white columns represent the durations of immobility during the final 4 min for Ctr1 and 3-NP1, respectively. * $P < 0.05$.

Fig. 2 The second set of experiments demonstrating the duration of immobility of mice at day 15 after 3-NP intoxication and the effect of DMI. White and slight black columns depict the durations of immobility during the final 2 min in modified FST-1 at day 15 post-intoxication without (for Ctr2 and 3-NP2) or with (for Ctr3 and 3-NP3) DMI treatment, respectively. ** $P < 0.01$.

received DMI in 3-NP3 was significantly shorter compared to the mice in 3-NP2 without DMI treatment [$F(1, 23) = 9.808$, $P = 0.005$].

3.3 The third set of experiments In 3-NP4, one mouse died at day 6 post-intoxication, the residual 10 mice displayed motor impairment at day 6 (Table 1), similarly but varied slightly in severity compared to that observed in mice of 3-NP1. These 10 mice did not show any sign of motor deficits by day 15, and were used for further experiments. Figure 3 showed that the durations of immobility for mice from both groups in the second modified FST-2 were significantly longer than those in the first modified FST-2, because of the experience just 24 h ago [for Ctr4: $F(1,12) = 10.96$, $P = 0.006$; for 3-NP4: $F(1,18) = 20.381$, $P = 0.000$]. Given that the duration of immobility in mice that are trapped and forced to swim is closely related to helplessness^[23,24], the 3-NP treatment does not prevent “learned helplessness” from happening. Moreover, it is unexpected that the experienced mice which just recovered from 3-NP-intoxication, still float significantly longer than the experienced control mice in the second modified FST-2 [$F(1,15) = 10.68$, $P = 0.005$].

Fig. 3 The third set of experiments illustrating the duration of immobility of mice at day 15 and day 16 after 3-NP intoxication. White columns and the slight black columns depict the durations of immobility during the whole 4 min in modified FST-2 at day 15 and day 16 (24 h later) post-intoxication, respectively. * $P < 0.05$; ** $P < 0.01$.

4 Discussion

The early striatum change in HD patients was suspected to be involved in series of neuropsychiatric symptoms, such as cognitive impairment, apathy, and depression, which pre-date the onset of motor deficits by 2 to 20 years^[12-17]. Researches in HD transgenic mouse models show that mild cognitive deficits precede motor abnormalities, but the depressive-like behavior was not studied yet in these pre-

symptomatic HD mice^[27,28]. Our experiments were tried to test the depressive-like behavior in the 3-NP mouse model, but the experiments was designed and performed in the opposite way, namely, the depressive-like behavior was observed in mice that recently recovered from motor deficits.

The 3-NP intoxication in striatum renders animals to sub-acute motor disorder, but most of affected animals, as predicted, can recover from the motor deficit rapidly and remarkably. In our experiments, at day 15 after 3-NP intoxication, mice used in FST did not show motor symptoms anymore but presented depressive-like behavior as indicated by the changed duration of immobility. The depressive-like behavior could be effectively counteracted by the antidepressant, DMI. At day 45 post-intoxication, the mice totally revitalized and did not show depressive-like behavior at all. The depressive-like behavior or state does not appear to be related to the fatigue or general sickness after 3-NP intoxication, as the duration of immobility for 3-NP treated mice was increased more significantly in modified FST-I, in which mice was forced to swim for only 4 min, 2 min less than the program in routine FST^[24,26,29]. According to the literatures, the recognition dysfunction could be seen in animals that systemically received 3-NP, and was dose-dependent^[19]. Memory process was involved to explain immobility of animals^[29]. In our third set of experiments, the post-intoxicated mice at day 15 showed similar “learned helplessness”, compared to those in control group, indicating that the depressive-like state might occur independently without the involvement of cognitive defects. Meanwhile, in Y-maze, a simple two-trial recognition test^[30], the mice at day 15 following 3-NP intoxication presented spatial recognition memory same as the controls (the data not shown). Altogether, our findings suggest that a novel depression animal model may be established in mice that are in the initial period of recovery from 3-NP intoxication.

The novel depression mouse model might be helpful and beneficial for the pathogenesis research of the heterogeneous depressive disorder. As the motor defects disappeared in mice at day 15 post-intoxication in our experiment, the striatum damage, such as cytotoxic and vasogenic edema, induced by 3-NP treatment, had lessened^[20], or some replacement mechanisms had started working. The neuropathological changes could not improve so rapidly and dramatically, and at least mild striatal lesions should still exist at that

moment. Therefore we propose that the lessened striatum damage may underlie the depressive-like behavior. Our results support the clinical findings and the possible role of striatum in the pathogenesis of depression. However, other brain regions, such as hippocampus and frontal cortex, might also be damaged to some extent in the 3-NP animal model^[19,22,31]. These brain areas, in addition to striatum, should also be paid attention to in the further morphological or histological research.

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3-硝基丙酸中毒小鼠恢复运动功能后呈现抑郁样症状

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摘要 目的 纹状体可能与抑郁症的发生有关,但是目前还没有动物实验模型支持纹状体在抑郁症发病过程中的可能作用的证据。本研究在选择性损伤纹状体的3-硝基丙酸(3-NP)中毒动物实验模型上,观察小鼠是否出现抑郁样症状。**方法** 采用亚急性系统给予3-NP的方式制作小鼠实验模型,用强迫游泳实验(forced swimming test, FST)中的漂浮时间评价小鼠的抑郁样症状。**结果** 在注射3-NP后的15天,即小鼠完全恢复运动功能后的早期,小鼠在FST中的漂浮时间较对照组明显延长。这种抑郁样症状不是由于3-NP中毒后引起的疲劳或虚弱所造成,可被抗抑郁药去甲丙米嗪消除。在间隔24 h的两次FST中,可在24 h后(3-NP中毒后16天)FST中再次观察到这种抑郁样症状,小鼠还显示如常的习得性无助反应。**结论** 在3-NP中毒恢复期小鼠可建立一种新型的动物抑郁模型,小鼠的抑郁样症状可能不涉及认知缺陷而独立存在,而纹状体的损伤可能与3-NP中毒后抑郁样症状的产生有关。

关键词: 3-硝基丙酸; 强迫游泳实验; 抑郁; 纹状体; 小鼠