No spatial memory deficit exists in Kunming mice that recently recovered from motor defects following 3-nitropropionic acid intoxication

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Abstract: Objective Numerous studies have described both motor defects and cognitive impairments in several strains of rodents following 3-nitropropionic acid (3-NP) intoxication. In the present study, we investigated spatial recognition memory in Kunming mice that just recovered from motor defects induced by 3-NP. **Methods** Mouse model was made by systemic subacute 3-NP treatment, and spatial recognition memory was measured through the Y-maze Test, a simple two-trial recognition test. **Results** (1) On day 15 following 3-NP treatment, affected Kunming mice did not show motor defects in the Rotarod test and presented normal gait again. (2) In the following Y-maze test after 1h interval, the percentage (90.0%) of mice showing novel arm preference in 3-NP treatment group was significantly higher than the random chance level (50%), although it was only slightly higher than that (83.3%) in control group. On day 45 after 3-NP treatment, mice failed to choose unfamiliar novel arm as first choice, and the same occurred in the control group. (3) For both post-intoxicated (on day 15 and day 45 following 3-NP treatment) and control groups, the duration in the novel arm and the frequency of entering it, were longer and higher compared with familiar start and other arms. For these mice that recently recovered from motor defects following 3-NP intoxication, no spatial memory deficits were observed through Y-maze Test. **Conclusion** Kunming mice used in our assays might possess resistance to cognitive impairment induced by 3-NP, which is consistent with previous findings in Swiss EPM-M1 mice.

Keywords: 3-nitropropionic acid; neurotoxicity; memory deficit; Kunming mouse; Y-maze

1 Introduction

3-Nitropropionic acid (3-NP) is a widely known plant-borne and fungal toxin, which could induce neurotoxicity^[1-4]. Systemic administration of 3-NP not only causes motor disorders in most rodents, but also induces cognitive deficits in several strains of rodents, especially with a form of prolonged treatment^[5-9].

Fernagut *et al.* found that systemic subacute administration of 3-NP in C57BL/6 mice induced a distinct motor disorder, but most affected mice strikingly recovered from

this motor disorder within 7-10 days^[2]. Our recent data were consistent with their observations. Most of our Kunming mice affected by systemic subacute 3-NP treatment recovered from the motor deficit rapidly and remarkably, without showing motor defects in the Rotarod test, and presented a normal gait again on day 15 after 3-NP treatment^[10]. Meanwhile, we found that these mice showed similar “learned helplessness” symptoms compared to control mice in the forced swimming test^[10]. Using Y-maze, a simple two-trial recognition test^[11-13], we further investigated whether the post-intoxicated Kunming mice presented spatial recognition memory deficits on day 15 and 45 following 3-NP treatment.

2 Materials and methods

2.1 Animals Kunming mice (10 weeks old, male, strain from Laboratory Animal Centre, Tongji University, Shanghai, China)

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Article ID: 1673-7067(2009)02-0087-07
CLC number: Q427
Document code: A
Received date: 2009-01-05

were used throughout the experiments. Mice were housed at room temperature $23 \pm 2^\circ\text{C}$, with relative humidity $55 \pm 10\%$ and a 12-h alternating light-dark schedule. They were free to food pellets and water. Before any behavioral assessment, there was at least one week's adaption to the laboratory environment. All studies were carried out in accordance with the guideline of the China Council on Animal Care. Efforts were made to minimize animal's suffering and to reduce the number of animals used.

2.2 Administration of 3-nitropropionic acid Sixteen mice were randomly assigned into two groups. 3-NP (analytical grade, Sigma-Aldrich, USA) was dissolved in normal saline to concentration of 8 mg/mL. Each mouse in 3-NP group ($n=10$) received 3-NP i.p. injections twice per day, 12 h apart with the following schedule: $20\text{ mg/kg} \times 4$, $40\text{ mg/kg} \times 6$ (total cumulated dose 320 mg/kg for 5 d). This intoxication paradigm was a modification based on the report of Fernagut *et al.*^[2], and would induce striatal lesions and a distinctive motor disorder in C57BL/6 male mice aged 16-20 weeks. Each mouse in control group ($n=6$) received i.p. vehicle injections with the same volume and the same time schedule as 3-NP group.

2.3 Rotarod The procedure of the Rotarod was based on previous studies with some modifications^[2,10,14]. Briefly, mice were placed on a stationary rod (diameter = 70 mm) and were trained to stay on it as the rod rotated at 5 r/min. Usually 4 to 6 training sessions on consecutive days (each constituted by a maximum of 10 trials) were needed to achieve the maximal performance, which took 180 s. By the end of the training period, each mouse had reached the skill level of 180 s on its first run. During 3-NP intoxication process, mice were retested once per day. In days 6 to 15 post-intoxication, mice were retested once every other day. The mean time that mice spent staying on the rotating rod in three consecutive trials was used as the assessment criterion of competency in this skill test.

2.4 Y-maze test The Y-maze consists of three arms with an angle of 120° between each. Arms are identical, and each is 8 cm in width, 40 cm in length and 15 cm in height. The three arms were randomly designated: Start arm, in which the mouse started to explore (always open); Novel arm, which was blocked at the first trial, but open at the second trial, and

Other arm (always open). The maze was placed in a sound-attenuated room under dim illumination. Floor of the maze was covered with sawdust. After each trial, the sawdust was mixed; the objects were cleaned in order to eliminate olfactory stimuli. Visual cues were placed on the walls of the maze.

The Y-maze test consisted of two trials separated by a 1 h time interval to assess spatial recognition memory^[11-13]. In the first trial, novel arm of Y-maze was blocked, mouse was placed in the start arm, with its head pointing against the center of the maze. It was allowed to visit the two arms (start and other arm) for 10 min. During the second trial, mouse was placed back to the start arm, with free access to all three arms for 5 min. The second trials was recorded by a ceiling-mounted video camera. Data were analyzed and expressed as (1) the percentage of novel arm as first choice (as discrimination memory measure); (2) the percentage of duration in novel arm compared to the other arms in the 5-min retention phase (as spatial recognition memory measure); (3) the percentage of number of visits in each arm during the 5-min retention test (as an index of inquisitive behavior); (4) the total number of entries in three arms during the 5-min retention test (as a locomotor activity index).

2.5 Statistical analysis All data were expressed as mean $\pm$ SEM and analyzed using the SPSS statistical software package (version 13.0). Percentages of the first choices in the novel arm were compared to chance (50%) with the Chi-squared test (χ^2). Differences between groups for percentage of duration and number of visits in the novel arm, and the difference between the three arms (novel, start and other) were assessed with analysis of variance (ANOVA). $P < 0.05$ was considered statistically significant. One-way ANOVA was used to analyze the difference between the three arms. Post hoc between-group comparisons were completed with Fisher's Least Significant Difference test (LSD). Differences of Rotarod test performance, the body weight and the total number of arm entries between groups with or without 3-NP treatment were analyzed by student's *t*-test.

3 Results

3.1 Motor disorders induced by 3-NP treatment In 3-NP group, all the 10 mice developed motor disorders at day 6

post-intoxication, with symptoms from slight motor slowing, transient hindlimb dystonia to long-term hindlimb dystonia, kyphosis, hindlimb claspings, and even global postural adjustment impairment. Rotarod test demonstrated significant deficits on day 6 following 3-NP treatment, compared to the baseline performances and control group. However, on day 15 following 3-NP treatment, all these mice recovered from the motor disorders and presented a normal gait again, showing no significant difference with baseline performances or with the control group in the Rotarod test. Either, there was no significant difference in body weight between the two groups (Table 1).

3.2 The performance in Y-maze test at day 15 and 45 post intoxication

3.2.1 The percentage of novel arm selection as the first choice

As shown in Fig. 1, the percentage of novel arm as the first choice in Group 3-NP mice at day 15 post-intoxication was 90% ($n=10$, $\chi^2=6.4$, $P=0.011$), which was significantly higher than chance level (50%). However, the percentage of novel arm as the first choice in Group Ctr mice was 83.3% ($n=6$, $\chi^2=2.667$, $P=0.102$), which was slightly less than the one in Group 3-NP mice and was not significantly different with chance level. At day 45 post-intoxication, neither Group 3-NP ($n=10$, $\chi^2=0.004$, $P=0.527$) nor Group Ctr ($n=6$, $\chi^2=2.667$, $P=0.102$) mice chose the novel arm as the first choice, with no significant difference with chance level.

3.2.2 The percentage of arm duration in the 5-min retention test

As shown in Fig. 2, both Group 3-NP ($F(2, 27)=11.686$, $P<0.001$) at day 15 post-intoxication and Group Ctr ($F(2, 15)=12.246$, $P<0.001$) mice showed higher percentages of

Fig. 1 Percentage of the first choice in the novel arm in mice with or without 3-NP treatment in 5-min Y-maze test. The dotted line represents the chance level (50%). In Group 3-NP at day 15 post-intoxication, the percentage of novel arm as first choice was significantly higher than chance level. $*P<0.05$.

Fig. 2 The percentage of duration in the novel, start and other arms in the Y-maze test. The percentage of duration for both Group 3-NP and Group Ctr mice visiting the novel arm was higher than the start and other arms at day 15 and 45 post-intoxication. $*P<0.05$, $**P<0.01$.

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

Groups	Rotarod (mean time, s)			Body weight (g)	
	Baseline	Day 6	Day 15	Baseline	Day 15
Ctr	162.7±14.3	172.8±15.7	176.7±3.2	44.6±2.2	46.8±2.6
3-NP	163.5±16.2	73.8±18.9**	171.2±5.1	44.7±1.9	45.9±2.8

Rotarod tests in 3-NP-intoxicated mice (Group 3-NP, $n=10$) compared to vehicle-injected animals (Group Ctr, $n=6$) were performed at baseline, then at day 6 and day 15 post-intoxication. The body weight of mice in Group 3-NP, compared to Group Ctr, was determined at baseline, then at day 15 post-intoxication. $**P<0.01$.

duration in novel arm than in other arm. Post hoc analysis with LSD showed significantly higher percentage time in the novel arm vs. the start arm ($P<0.001$) and vs. the other arm ($P<0.001$). The percentage time in novel arm was also higher than that in the other arms in both Group 3-NP ($F(2, 27)=6.123$, $P=0.006$; LSD: novel arm vs. start arm, $P=0.013$; novel arm vs. other arm, $P=0.003$) at day 45 post-intoxication and Group Ctr ($F(2, 15)=9.412$, $P=0.002$; LSD: novel arm vs. start arm, $P=0.002$; novel arm vs. other arm, $P=0.002$).

Moreover, the 5-min retention test revealed that neither the 3-NP group at day 15 nor the 3-NP group at day 45 post-intoxication exhibited any significant difference in percentage time in novel arm, as compared with control group (day 15, $F(1,14)=0.253$, $P=0.623$; day 45, $F(1,14)=1.724$, $P=0.210$).

3.2.3 The percentage of number of arm visits in the 5-min retention test As shown in Fig. 3, a higher number of novel arm entries compared to other arms was found in both 3-NP group at day 15 post-intoxication ($F(2, 27)=14.469$, $P<0.001$; LSD: novel arm vs. start arm, $P=0.003$; novel arm vs. other arm, $P<0.001$) and control group ($F(2, 15)=5.264$, $P=0.019$; LSD: novel arm vs. start arm, $P=0.037$; novel arm vs. other arm, $P=0.007$) mice. This difference also occurred in both 3-NP group at day 45 post-intoxication ($F(2, 27)=17.627$, $P<0.001$; LSD: novel arm vs. start arm, $P<0.001$; novel arm vs. other arm, $P<0.001$) and control group ($F(2, 15)=25.389$, $P<0.001$; LSD: novel arm vs. start arm, $P<0.001$; novel arm vs. other arm, $P<0.001$). However, there was no significant difference in the percentage of novel arm visiting numbers, between the Group 3-NP and Group Ctr at day 15 ($F(1,14)=0.002$, $P=0.965$) and day 45 ($F(1,14)=0.801$, $P=0.386$) post-intoxication, respectively.

3.2.4 The total number of entries in the 5-min retention test

As shown in Fig. 4, there was no significant difference in total number of arm entry between Group 3-NP at day 15

Fig. 3 The percentage of numbers for mice visiting the novel, start and other arms in the Y-maze test. The percentage of numbers for both Group 3-NP and Group Ctr mice visiting the novel arm was higher than the start and other arms at day 15 and 45 post-intoxication. * $P<0.05$, ** $P<0.01$.

Fig. 4 Total number of entries in the novel, start and other arms for mice in the Y-maze test. The Group 3-NP mice at day 45 post-intoxication showed a significantly higher number of entries than Group Ctr. ** $P<0.01$.

post-intoxication and Group Ctr mice ($t(14)=1.771$, $P=0.098$). However, Group 3-NP at day 45 post-intoxication showed much higher total arm entry number than Group Ctr ($t(14)=4.469$, $P=0.001$).

4 Discussion

Our results demonstrated that mice recently recovered from motor defects following 3-NP intoxication did not show any spatial recognition memory deficits in the Y-maze.

The preference for novel arm is supposed to indicate the spatial discrimination memory^[13]. In 5-min retention test, mice have to make a choice between the novel arm (unfamiliar) and the other arm (familiar) when they walk out of the start arm in the Y-maze. Neither the post-intoxicated mice at day 45 following 3-NP treatment nor control mice were able to discriminate between the unfamiliar novel and the familiar other arm after 1 h interval, reflected by the finding that percentages of the first choice for the novel arm were not significantly different from random chance levels. Surprisingly, post-intoxicated mice at day 15 following 3-NP treatment even showed a little higher level in spatial discrimination memory than Group Ctr. The percentage of duration in novel arm compared to the other arms minute by minute in the 5-min retention is supposed to measure spatial recognition memory^[13]. Post-intoxicated mice at day 15 and 45 following 3-NP treatment showed a similar percentage of duration of visits in

three arms as Group Ctr mice did. For both 3-NP group (at day 15 and 45 post-intoxication) and control group, the time mice spent in the novel arm was more than that in the start and other arms after 1 h interval. The number of visits in each arm represents an index of inquisitive behavior^[13]. The similar percentage of number of arm entries indicated that post-intoxicated mice both at day 15 and 45 following 3-NP treatment showed an inquisitive behavior similar with their control group.

Previous studies reported that 3-NP treated animals exhibited simultaneously both motor disorders and cognitive impairment in the behavioral assessments^[6-9,15,16]. We did not detect the cognitive function while mice clearly showed motor defects (such as motor slowing, hindlimb dystonia, kyphosis and global postural maladjustment) following 3-NP intoxication, since it was hard to exclude the possibility that the motor defects could influence the cognitive performance in the Y-maze test.

Regarding the absence of memory deficit induced by 3-NP treatment, our data are in line with previous studies^[17,18], in which 3-NP systemically treated Lewis rats and Swiss EPM-M1 mice did not exhibit learning deficits in the discrimination tests. The susceptibility to the neurotoxic effects of 3-NP administration is strain dependent^[19,20]. In rat and mouse strains, Lewis rat and C57BL/6 mouse were reported to respond poorly to 3-NP toxicity^[19,20]. The impaired cognitive performance following 3-NP treatment could be detected in Wistar and Sprague-Dawley rats^[9,21,22], but not seen in Lewis rats^[17,22]. Therefore, we postulate that genetic factors might influence the cognitive performance following 3-NP intoxication. The Kunming mouse is an outbred stock derived from Swiss albino mice, and is widely employed in studies on neuroscience, genetics and pharmacology in Chinese laboratories^[23]. In respect to the motor disorders following the 3-NP treatment, the performance of the post-intoxicated Kunming mice in our previous studies was similar to the C57BL/6 mice^[10]. Given the research of cognition impairment following the 3-NP treatment, it seems that Kunming mice are not very sensitive.

The number of arm visits not only represents an index of inquisitive behavior, but also measures locomotor activity^[13].

In our experiments, locomotor activity in mice at day 45 post-intoxication was increased compared with the Group Ctr mice as shown by the increased total number of visits in three arms. It is consistent with the studies of Keene *et al.*^[21], who reported that 3-NP treated rats exhibited increased activity levels in the retest at 6 months following the injections. Keene *et al.* suggested that the increased activity was related to the cognitive impairment, due to the findings that cognition intact rat would habituate the environment, which resulted in reduced overall activity^[21]. However, other researchers analyzed that the increased activity might be a consequence of the animals' preservative behavior, which could be interpreted as an inability to inhibit ongoing action^[17]. Our data support the preservative behavior hypothesis because the hyperactive mice at day 45 following 3-NP treatment did not show spatial memory deficits.

Mice in our experiments, aged at 10 weeks, are very young. A direct correlation between animal age and neural damage in 3-NP rodent model has been demonstrated in several previous studies^[1,24,25]. In rodents less than 6 weeks old, systemic 3-NP injection had no adverse effects, while in older rodents aged over 7 weeks, more severe striatal damage was demonstrated^[1]. Lohmann and Riepe found that spatial learning ability was far less affected in the young (4.5 months) CD-1 mice treated with 3-NP than the middle-aged (9 months)^[26]. However, mice treated with 3-NP at a young age showed "delayed" learning deficits in old (22 months) age^[26]. Early adverse events, such as lead exposure in adolescence, may cause neurodegeneration in later life^[27]. It is worthy studying further whether much early 3-NP treatment in mice around 10 weeks old also induces a great susceptibility to learning deficits and neurodegeneration in old age.

Taken together, mice just recovered from motor disorders induced by 3-NP did not show spatial memory deficits in the Y-maze. We conclude that some strains of rodents, including Kunming mouse used in our experiments, might be resistant to the cognitive impairment induced by 3-NP.

Acknowledgement: This work was supported by the Medical Research Foundation of Tongji University, China (No.1509219020).

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3- 硝基丙酸中毒昆明小鼠恢复运动功能后没有空间记忆缺陷

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摘要: 目的 许多研究表明,啮齿类动物品系在3-硝基丙酸(3-NP)中毒后,有运动与认知两方面的损伤。本文旨在研究3-NP中毒的昆明小鼠在运动恢复后的空间认知记忆状况。**方法** 采用亚急性系统给予3-NP的方式制作小鼠实验模型,并通过Y-迷宫,简单双试法来测定空间认知记忆水平。**结果** (1)3-NP处理后15 d,受损昆明小鼠步态正常,在转杆测试中不再显示运动缺陷;(2)间隔1 h后进行Y-迷宫测试,经过3-NP处理后15 d小鼠对新臂的偏好(90.0%)显著高于随机水平(50.0%),仅稍高于对照组(83.3%),而3-NP处理后45 d小鼠及对照组小鼠首选不熟悉的新臂状况与随机水平没有显著差异;(3)不管是中毒后小鼠(分别为3-NP处理后15天及45天)还是对照组小鼠,在新臂的停留时间及反复进入新臂的次数均显著高于熟悉的起始臂和其他臂。在对3-NP中毒后运动恢复了的小鼠进行Y-迷宫测试没有观察到空间记忆障碍。**结论** 结果提示本实验所使用的昆明小鼠可能对于3-NP所致认知缺陷存在耐受性,3-硝基丙酸中毒昆明小鼠恢复运动功能后没有空间记忆缺陷,这与早期在Swiss EPM-M小鼠上的发现相一致。**关键词:** 3-硝基丙酸;神经毒性;记忆缺陷;昆明小鼠;Y-迷宫