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Gender-specific impairments on cognitive and behavioral development in mice exposed to fenvalerate during puberty

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ABSTRACT

In human and rodent models, endocrine disrupting chemicals (EDCs) interfere with the development of cognition and behaviors. Fenvalerate is a potential EDC. The purpose of this study was to examine whether pubertal fenvalerate exposure altered behavioral development. Mice were orally administered with either vehicle or fenvalerate (7.5 or 30 mg/kg/day) from postnatal day (PND) 28 to PND56. Learning and memory were assessed by Morris Water Maze. Aggressive performance was evaluated by aggressive behavior test. Anxiety-related activities were detected by three tests: open-field, plus-maze and black-white alley. Sensorimotor function was analyzed using beam walking and tightrope. Results found that the impairment for spatial learning and memory was more severe in fenvalerate-exposed female mice than in male mice. In addition, pubertal fenvalerate exposure inhibited aggressive behavior in males. Moreover, pubertal fenvalerate exposure increased anxiety activities in females. Altogether, these results suggest that pubertal fenvalerate exposure impairs spatial cognition and behavioral development in a gender-dependent manner. These findings identify fenvalerate as candidate environmental risk factors for cognitive and behavioral development, especially in the critical period of development.

1. Introduction

In human and rodent models, androgen or estrogen in the brain profoundly plays a critical role in sexual differentiation of brain and behaviors during developmental period (Paus et al., 2010; Bodo and Rissman, 2007). Several studies showed that cognition and anxiety-related behaviors in males were altered by testosterone (T), which acted not only through androgen receptor (AR) but also through estrogen receptors (ERs) (Frye et al., 2008a,b; Zuloaga et al., 2008). Another study found that conditional inactivation of AR in the nervous system, areas involved in cortex and hippocampus, inhibited sexual motivation and performance as well as aggressive behaviors in male mice (Raskin et al., 2009). Data from knock-out (KO) mice ubiquitously lacking CYP19 (aromatase) or ERα indicated that E_2 deriving from neural aromatization of T and ER signaling pathway might play an important role in sexual and aggressive behaviors (Bakker et al., 2002). Interestingly, a recent study reported that CYP19 gene polymorphism affected personality trait of harm avoidance in healthy population (Matsumoto et al., 2009).

On the other hand, there is growing concern for adverse health outcomes resulted from endocrine disrupting chemicals (EDCs). Numerous animal data showed an impairment on cognitive, sex-related or anxiety-related behaviors in animals developmentally exposed to EDCs, such as polychlorinated biphenyls (PCB, Colciago et al., 2006, 2009) bisphenol A (BPA, Rubin et al., 2006; Palanza et al., 2008; Brown, 2009), dioxin (Hojo et al., 2006). Moreover, several human investigations found that prenatal exposure to phthalate (Engel et al., 2010), PCB (Park et al., 2009) and phthalate (Swan et al., 2010) were associated with subsequent childhood mental and behavioral development. These evidences suggest that it should be focus on the impairment neurodevelopment induced by EDCs.

Recently, fenvalerate, a widely used pyrethroid insecticide, has been demonstrated to have endocrine disruptive effects. An epidemiological report showed statistically significant relationships between pyrethroid insecticide metabolite concentrations and circulating T levels among nonoccupational population in China (Han et al., 2008). Another recent study found the level of androgen was decreased, which was relative to urinary metabolites of pyrethroid insecticides among the US general population (Meeker et al., 2009). Similarly, early animal data have showed that perinatal exposure

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to fenvalerate significantly reduced plasma level of T or E_2 and delayed sexual maturation in the male and female offspring (Moniz et al., 1999, 2005). Further studies demonstrated that fenvalerate inhibited the release of T and E_2 by reducing the expression of steroidogenic acute regulatory protein (StAR) and cytochrome P450 side-chain cleavage (P450scc), and then exerted estrogenic and/or anti-androgenic activity (Fei et al., 2010; Xu et al., 2006). According to our recent studies, the level of serum and testicular T was significantly decreased in mice exposed to fenvalerate during gestation, location or puberty (Zhang et al., 2009, 2010a,b). Furthermore, our study found that pubertal fenvalerate exposure disrupted T and E_2 synthesis and the expression of AR in developing brain (Liu et al., 2011). However, the potential effect of fenvalerate on cognitive function and behavioral development remains unclear.

The aim of present study was to examine whether pubertal exposure to fenvalerate altered spatial cognition and behavioral development in mice. We found that pubertal fenvalerate exposure impaired spatial cognition and behavioral development in a gender-dependent manner. That is, spatial learning and memory was more severely impaired in female mice than in male mice. In addition, aggressive behavior was inhibited in fenvalerate-exposed male mice. Moreover, anxiety-related activities were increased in fenvalerate-exposed female mice.

2. Materials and methods

2.1. Animals and treatment

ICR mice (3-week-old) were purchased from Beijing Vital River whose foundation colonies were all introduced from Charles River Laboratories, Inc. They were maintained on a 12-h light/dark cycle in a controlled temperature (20–25 °C) and humidity (50% ± 5%) environment for one week before use. Food and water were provided *ad libitum*. Animals were treated humanely and with regard for alleviation of suffering according to protocols approved by the Association of Laboratory Animal Sciences and the Center for Laboratory Animal Sciences at Anhui Medical University.

To investigate the effects of pubertal fenvalerate exposure on neurobehavioral development, forty-eight mice (twenty-four males and twenty-four females) were randomly divided into three treatments (eight males and eight females each group). Our previous studies showed that no signs of toxicity were observed in mice treated with 30 mg/kg or a higher dose of fenvalerate (Zhang et al., 2009, 2010a,b). So in the present study, the dose of 30 mg/kg, about 1/8 LD50 of the fenvalerate, was administered in the high dose group. In the two fenvalerate treatments, mice were administered with different doses (7.5 or 30 mg/kg) of fenvalerate (Sigma Chemical Co., St. Louis, MO) by gavage daily from PND28 to PND56. The corn oil treated mice served as controls. After treatment with fenvalerate for four weeks, a battery of behavior tests were performed.

2.2. Behavioral tests

In the present study, the behaviors were grouped into related categories, such as learning and memory, aggressive performance, anxiety-related activities, and sensorimotor function. Learning and memory were assessed by Morris Water Maze. Aggressive performance was assessed by aggressive behavior test. Anxiety-related activities were detected by three tests: open-field, black-white alley and elevated plus-maze. Sensorimotor function was evaluated using beam walking test and tightrope test. In order to minimize stress or interference by each other, the order of actual tests was: open-field, black-white alley, elevated plus-maze, beam walking, tightrope, aggressive behavior test, Morris Water Maze.

2.2.1. Morris Water Maze

Spatial learning and memory was assessed by Morris Water Maze (Morris, 1984) from PND67 to PND73. Briefly, the apparatus used was a circular black tank (150 cm diameter, 30 cm high). It was filled with water at room temperature (25 ± 1 °C) to a depth of 25 cm. The escape target was a black platform (diameter 10 cm), which was submerged 1 cm below the water surface. It included two parts: spatial training trials and spatial probe test. In the spatial training trials, the animals were tested with 4 trials per day in place navigation task for 6 consecutive days. On the seventh day, the spatial probe test was conducted to test spatial memory. A video camera fixed at the ceiling above the tank and linked to a computer recorded the swim tracks, latency to find the platform, swim distance, swim speed and swim time in the objective quadrant.

2.2.2. Aggressive behavior test

Aggressive performance was assessed on PND66 by aggressive behavior test (Kawai et al., 2003). Clean polycarbonate mouse cages (17 cm × 28 cm × 13 cm) were used. The male mouse to be tested was placed alone in a neutral container for 5 min. The opponent mouse, age matched with the resident test animal, was introduced into the cage. Chasing, boxing, tail rattling, biting, and offensive attack (often accompanied by biting and wrestling) were defined as aggressive behavior acts. Each test was performed with a different intruder for 7 min in a dimly lit room at night. The recorded parameters were the latency of the first attacking and the cumulative time of aggression. The experimenters were trained in this method and not familiar with the treatment histories of the subject mice. Before the next mouse was tested, feces and urine were removed and the arena was thoroughly cleaned with water.

2.2.3. Open field

The protocol for open field was designed as previously described (Wang et al., 2010). The open-field apparatus was a black wooden box, 81 cm long, 81 cm wide, 28 cm high, enclosed arena. The box floor was painted with white lines (3 mm wide) to form 16 equal squares (20 cm × 20 cm) with a colored box (8 cm × 5 cm × 3 cm) in the center of the area. Illumination was provided by a 40-W white light placed 2.80 m above the center of the field. The individual mice were placed in a corner square, facing the walls and observed for 5 min. The following parameters were recorded: total number of squares crossed, latency to the first grid crossing and peripheral time (the time spent in the 12 peripheral squares). After each trial, the enclosure was cleaned with water.

2.2.4. Black-white alley

As previous literature described (Wang et al., 2010), the apparatus for black-white alley is a narrow galvanized iron box (120 cm × 9 cm × 30 cm, half was black and the other half was bright). Each mouse started in the less aversive black alley and was observed for 90 s. Recorded parameters were: latencies to enter (all four paws) into the opposite half, total time spent in the black half, number of crossings of the barrier, and the number of faecal boli. Between each mouse, feces and urine were removed and the apparatus was thoroughly cleaned up.

2.2.5. Elevated plus maze

As Lister's design (Lister, 1987), the maze was made up of two opposite enclosed arms (30 cm long, 5 cm wide, 15 cm high) and two opposite open arms (also 30 cm long, 5 cm wide, without edges) and had a central arena (5 cm × 5 cm). The whole apparatus was elevated 80 cm above the floor. Each mouse was successively placed in the central arena of the maze facing an open arm, and observed for 5 min. Recorded parameters were: time spent in the enclosed arms and the number of entries into the open arms. The maze was cleaned with water after each mouse.

2.2.6. Beam walking

Beam walking is a motor skill and balance test. The apparatus consisted of a wooden beam (51 cm long, 1 cm wide) and two vertical supports (50 cm high) above a round tank (150 cm diameter) (Wang et al., 2010). Each mouse was given three successive trials and perpendicularly placed on the center of the beam. Each trial was maintained for a maximum of 60 s. The mean time recorded for the three trials was used for statistical analysis.

2.2.7. Tightrope

The taut and tiny cotton rope (150 cm long, 2 mm diameter) was marked with ink at 5-cm intervals along its length. It was stretched across a round tank (100 cm diameter, 30 cm high) half-filled with water (at 19–22 °C) (Wang et al., 2010). Mice were placed with their front paws in the middle of the rope tightly. Recorded parameters were: the suspension time and the number of markers crossed. We used a transformed score [=(average suspension time) + 10(average number of the marker crossed) for statistical analysis.

2.3. Data analysis

All data were expressed as mean ± SEM. Data for the Morris Water Maze was analyzed by repeated-measures two-way ANOVA. Data for aggressive performance were analyzed by one-way ANOVA. Other data were analyzed by two-way ANOVA. The significance level was set at $P < 0.05$. All statistical analyses were performed using the statistical package for social sciences (SPSS, version 12.0).

3. Results

3.1. Effects of pubertal fenvalerate exposure on physical development in mice

Consistent with our previous reports (Zhang et al., 2009, 2010a,b), exposure of mice to fenvalerate at 30 mg/kg or 7.5 mg/kg by gavage daily from PND28 to PND56 did not negatively impact developmental outcomes or cause overt signs of intoxication. In

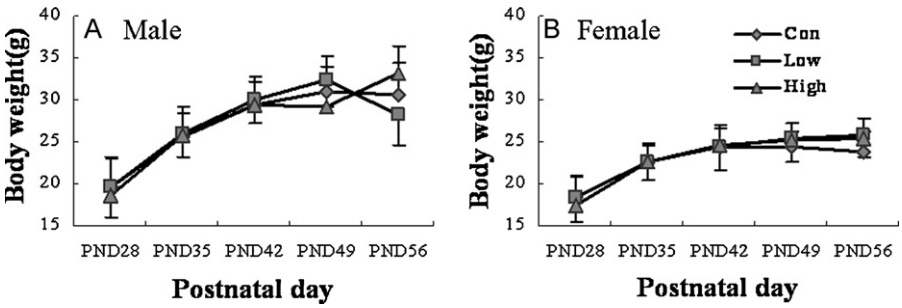

Fig. 1. Effects of pubertal fenvalerate exposure on body weight in mice. Mice were administered with fenvalerate (30 mg/kg or 7.5 mg/kg) by gavage daily from PND28 to PND56. (A) Body weight of male mice. (B) Body weight of female mice.

addition, the pubertal fenvalerate exposure had no effect on body weight of mice from PND28 to PND56 (Fig. 1).

3.2. Effects of pubertal fenvalerate exposure on spatial learning and memory

The effects of pubertal fenvalerate exposure on learning and memory performances were examined by Morris Water Maze. As expected, a significant difference on the escape latency was observed among different groups ($P < 0.01$). The escape latency in fenvalerate-treated female mice was longer than that of controls from day 2 through day 6, whereas there was no significant difference among male mice from different groups (Fig. 2A and B). Repeated measures indicated that escape latency was longer in fenvalerate-exposed female mice than controls (Fig. 3A, $P < 0.001$). Similarly, swim distance was longer in female mice treated with fenvalerate than controls (Fig. 3B, $P < 0.001$). We also found that times of crossing objective quadrant was decreased in fenvalerate-exposed female mice as compared with controls (Fig 3C, $P < 0.01$). In addition, the time proportion of objective quadrant was significantly decreased in female mice treated with 7.5 mg/kg of fenvalerate (Fig 3D, $P < 0.05$). By contrast, it is only in males but not in females that difference on swim speed and distance in objective quadrant was statistically significant. Further analyses showed that swim speed was obviously reduced in male mice treated with 30 mg/kg of fenvalerate (Fig. 3E, $P < 0.01$). In addition, the distance of the objective quadrant was significantly decreased in male mice exposed 30 mg/kg of fenvalerate (Fig. 3F, $P < 0.05$).

Spatial memory was assessed on the seventh day. It is only in female mice, but not in male mice, that differences on swim distance (female: $F_{(2,21)} = 4.96$, $P < 0.05$; male: $F_{(2,21)} = 0.20$, $P > 0.05$), times of crossing the objective quadrant (female: $F_{(2,21)} = 4.17$, $P < 0.05$; male: $F_{(2,21)} = 1.20$, $P > 0.05$) and the proportion of the time in objective quadrant (female: $F_{(2,21)} = 4.96$, $P < 0.05$; male: $F_{(2,21)} = 0.20$, $P > 0.05$) were statistically significant. Further analyses showed that swim speed was significantly decreased in female mice treated with 30 mg/kg of fenvalerate (Fig. 3G, $P < 0.05$), whereas times of crossing the objective quadrant was significantly reduced in female mice treated with 7.5 mg/kg of fenvalerate (Fig. 3H, $P < 0.05$). In addition, the proportion of the time in objective quadrant was also markedly reduced in all fenvalerate-exposed female mice (Fig. 3I, $P < 0.05$).

3.3. Effects of pubertal fenvalerate exposure on aggressive performance

As shown in Fig. 4, there was a significant difference in latency ($F_{(2,21)} = 4.21$, $P < 0.05$) and contact time ($F_{(2,21)} = 3.86$, $P < 0.05$) among different groups. Further analyses showed that latency was much longer in male mice treated with 30 mg/kg of fenvalerate than mice from other groups ($P < 0.05$). By contrast, contact time was much shorter in mice treated with 30 mg/kg of fenvalerate than mice from other groups ($P < 0.05$). However, no significant difference in latency and contact time was observed between mice treated with 7.5 mg/kg of fenvalerate and controls.

3.4. Effects of pubertal fenvalerate exposure on anxiety-related activities

The effects of pubertal fenvalerate exposure on exploration and anxiety activities were detected by three tests: open-field, elevated plus-maze and black-white alley. In the open-field test, there was no significant difference in latency and squares crossed (Fig. 5A and B). The effects of pubertal fenvalerate exposure on peripheral time

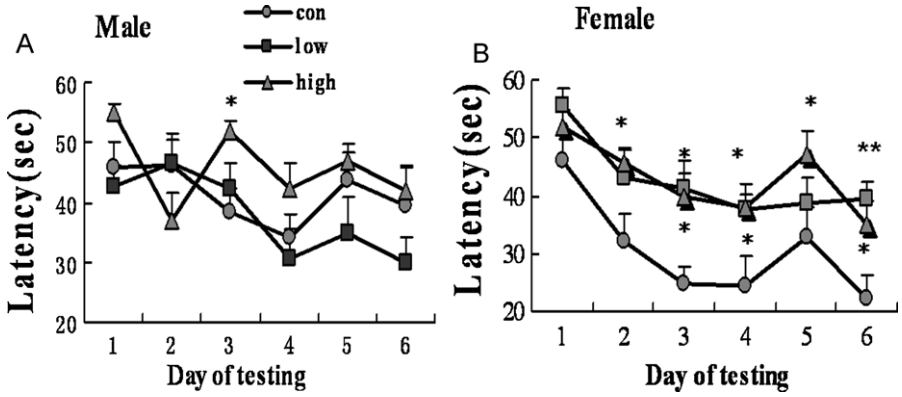

Fig. 2. Effects of pubertal fenvalerate exposure on learning performance during the 6-day training period. Mice were administered with fenvalerate (30 mg/kg or 7.5 mg/kg) by gavage daily from PND28 to PND56. Morris water maze was performed from PND67 to PND73. (A) Escape latency of male mice with the day of testing. (B) Escape latency of female mice with the day of testing. Data were presented as mean ± SEM. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ compared with the controls (A and B, ANOVA).

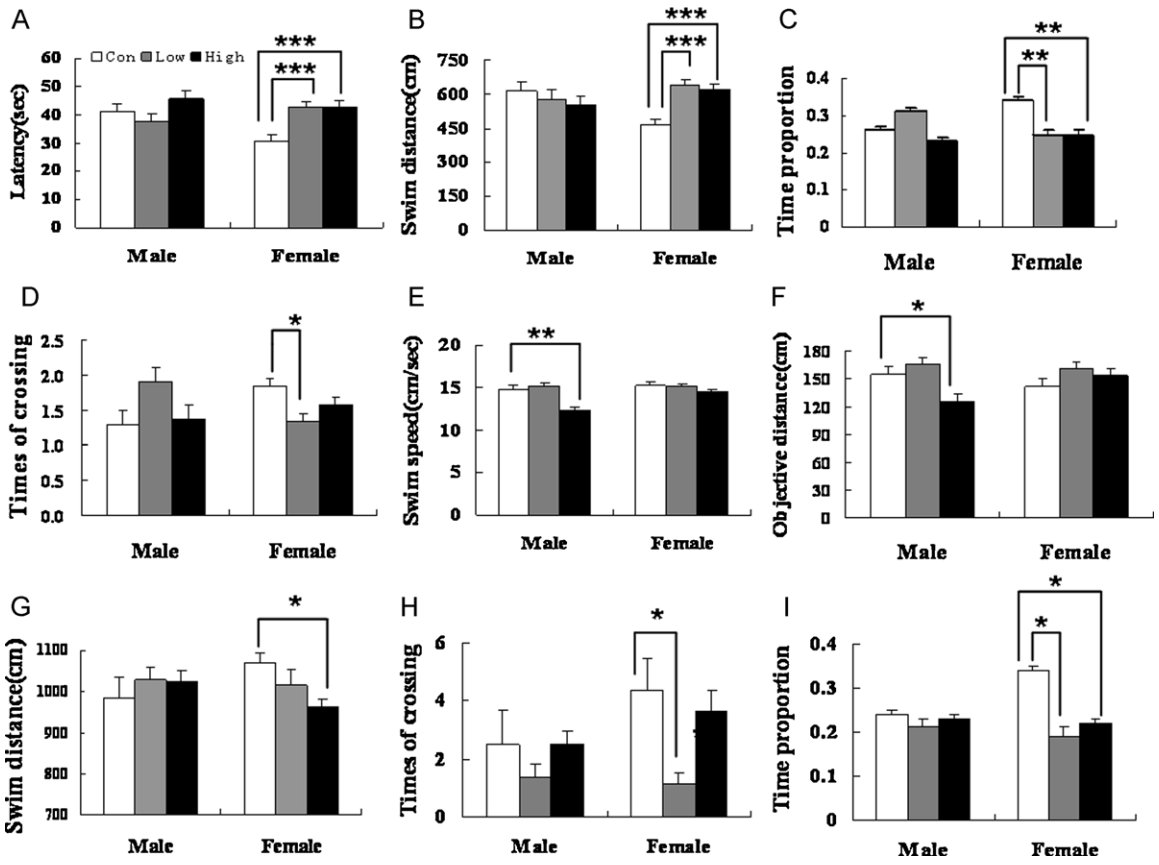

Fig. 3. Effects of pubertal fenvalerate exposure on learning and memory performance. Mice were administered with fenvalerate (30 mg/kg or 7.5 mg/kg) by gavage daily from PND28 to PND56. Morris water maze was performed on PND73. (A) Escape latency during the 6-day training period. (B) Swim distance during the 6-day training period. (C) Time proportion of the objective quadrant during the 6-day training period. (D) Times of crossing the objective quadrant during the 6-day training period. (E) Swim speed during the 6-day training period. (F) Distance of objective quadrant. (G) Swim speed on the seventh day. (H) Times of crossing objective quadrant on the seventh day. (I) Time proportion of objective quadrant on the seventh day. Data were presented as mean ± SEM. $^{*}P<0.05$, $^{**}P<0.01$, $^{***}P<0.001$ compared with the controls (A–F, repeated measures ANOVA; G–I, ANOVA; Bonferroni post hoc).

are presented in Fig. 5C. Peripheral time was significantly increased in female mice treated with 30 mg/kg fenvalerate ($P<0.01$). By contrast, peripheral time was significantly decreased in the male mice treated with 7.5 mg/kg ($P<0.05$). In the plus-maze, there were no significant differences in entries into open arms and time in open arms among different groups. In the black-white alley, the latency in male mice treated with 30 mg/kg of fenvalerate was significantly decreased as compared with male controls (Fig. 5D, $P<0.05$). Interestingly, fenvalerate-exposed male mice took shorter time to enter the white alley as compared with controls, whereas fenvalerate-exposed female mice took longer time to enter the white alley (Fig. 5D). There was no significant difference in the time in black alley and the number of crossing among different groups.

3.5. Effects of pubertal fenvalerate exposure on sensorimotor function

Sensorimotor function was evaluated using beam walking test and tightrope test. As shown in Fig. 6A, horizontal score was significantly different in male mice ($F_{(2,21)}=3.83$, $P<0.05$), but not in females ($F_{(2,21)}=0.27$, $P>0.05$). Further analyses showed that horizontal score in male mice treated with 30 mg/kg of fenvalerate was markedly decreased as compared with male mice exposed

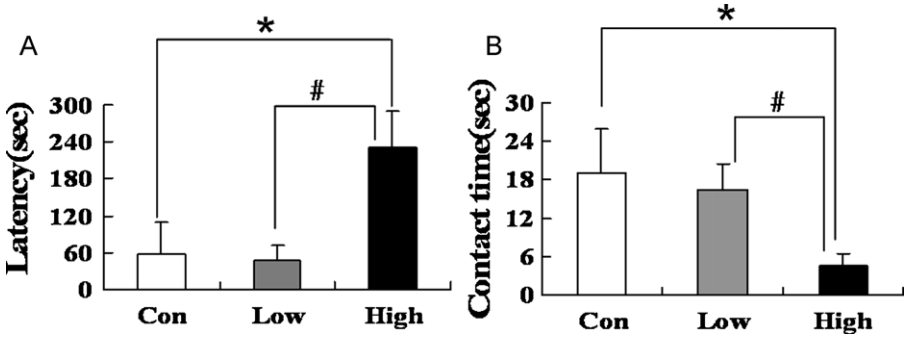

Fig. 4. Effects of pubertal fenvalerate exposure on aggressive performance. Mice were administered with fenvalerate (30 mg/kg or 7.5 mg/kg) by gavage daily from PND28 to PND56. Aggressive behavior test was performed at PND66. (A) Latency. (B) Contact time. Date was presented as mean ± SEM. $^{*}P<0.05$ compared with the controls. $^{\#}P<0.05$ compared with male mice treated with 7.5 mg/kg fenvalerate during puberty.

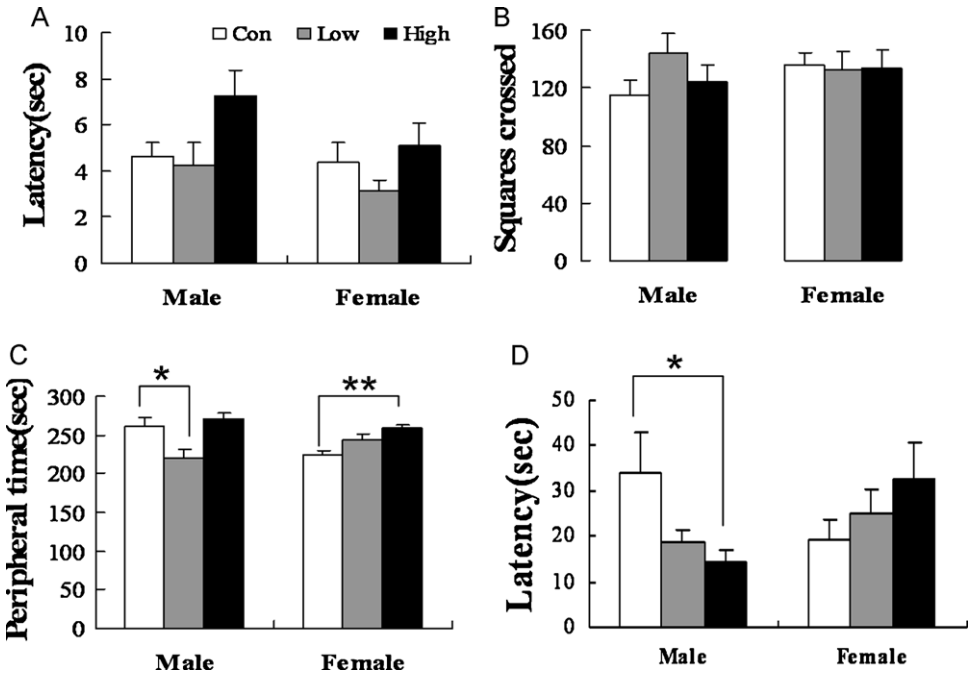

Fig. 5. Effects of pubertal fenvalerate exposure on exploration and anxiety activities. Mice were administered with fenvalerate (30 mg/kg or 7.5 mg/kg) by gavage daily from PND28 to PND56. (A) Latency to the first grid crossing in open-field test; (B) squares crossed in open-field test; (C) peripheral time in open-field test; (D) latency to enter the white alley in black-white alley. Data were presented as mean ± SEM. $^{*}P < 0.05$, $^{**}P < 0.01$ compared with the controls.

to 7.5 mg/kg of fenvalerate ($P < 0.05$). There was no statistically significant difference in tightrope score among different groups. However, a tendency of reduction on the tightrope score was observed in fenvalerate-exposed male mice. By contrast, there was a tendency of elevation on the tightrope score in fenvalerate-exposed female mice (Fig. 6B).

4. Discussion

In the present study, we carried out a series of behavioral tests to evaluate the effects of pubertal fenvalerate exposure on spatial cognition and behavioral development in mice. The major finding of this study is that pubertal fenvalerate exposure impaired cognitive and behavioral development in a gender-dependent manner.

Numerous reports have demonstrated that endocrine disruption could affect cognition in human and animals. A recent study found a positive correlation between T concentrations and spatial learning and memory performance in adult male white-footed mice (Pyter et al., 2006). According to a recent study, an important alteration in memory retention was noted specifically in male offspring whose mothers were chronically exposed to PBCs during pregnancy and lactation (Colciago et al., 2009). Similarly, perinatal genistein exposure impaired spatial learning in male rats (Ball et al., 2010). In the present study, we found that escape latency and swim distance in spatial learning phase were markedly increased in female mice exposed to fenvalerate during puberty. In addition, pubertal fenvalerate exposure reduced times of crossing objective quadrant and time proportion in objective quadrant in memory phase. These results suggest that pubertal exposure to fenvalerate impaired spatial learning and memory.

Increasing evidence has demonstrated that there are sex differences in spatial learning and memory, which may reflect hormonal effects on brain development (Newhouse et al., 2007; Paus et al., 2010; Woolley et al., 2010). Several studies reported that developmental exposure BPA, an estrogen-mimicking endocrine disruptor, significantly impaired the spatial recognition memory in both sexes, and modified behavioral coping in a gender-dependent manner (Poimenova et al., 2010). Indeed, sex differences in the performance of spatial tasks exist under physiological condition. Interestingly, the sex differences were decreased or eliminated in

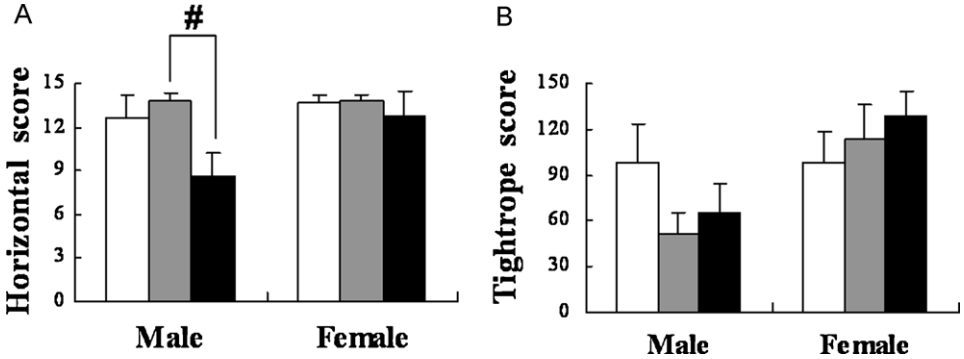

Fig. 6. Effects of pubertal fenvalerate exposure on sensorimotor function. Mice were administered with fenvalerate (30 mg/kg or 7.5 mg/kg) by gavage daily from PND28 to PND56. (A) Beam walking was tested on PND64. (B) Tightrope was tested on PND65. Data were presented as mean ± SEM. $^{*}P < 0.05$ compared with the 7.5 mg/kg fenvalerate group.

mice exposed to environmentally relevant levels of BPA (Palanza et al., 2008; Rubin et al., 2006). On the other hand, several earlier studies showed, in which male rats, unlike females, delayed learning and worse memory scores following exposure to restraint stress (Kitraki et al., 2004). In addition, female rats recovered quicker than their male counterparts from deficits in the Y-maze performance following chronic restraint stress (Conrad. et al., 2003). By contrast, the present study showed that fenvalerate-induced impairment in female mice was more severe than in male mice. Taken together, these results suggest that EDCs including fenvalerate might impair spatial learning and memory in a gender-specific manner.

Many studies demonstrated that endocrine disruption might alter the normal expression of aggressive behavior. A recent study showed that aggression was markedly higher in the combination "high T + high cortisol responses" in healthy men (Kuepper et al., 2010). An earlier study showed that differential perinatal T secretory capacity in testes of wild house mice was related to aggressiveness in adulthood (de Ruiter et al., 1993). Another study found that aromatization of T into E is important for the development of aggressive behavior (Wu et al., 2009). Fenvalerate is a potential endocrine disruptor, and exerts estrogenic and/or anti-androgenic activity (Zhang et al., 2009, 2010a,b). Thus, we hypothesized that exposure to fenvalerate during puberty could impair aggressive performance in male mice. As expected, the latency of aggressive behaviors was much longer in male mice exposed to fenvalerate during puberty. In addition, pubertal fenvalerate exposure significantly reduced the contact time in male mice, suggesting that aggressive behavior was impaired in male mice exposed to fenvalerate during puberty. Interestingly, aggression scores were significantly increased in male mice exposed to BPA, which mimics estrogenic activity (Kawai et al., 2003). In addition, neonatal exposure to BPA or phytoestrogen increased agonistic activity in adulthood (Patisaul and Bateman, 2008). These findings suggested that aggressive behavior were inhibited or increased in animals developmentally exposed to EDC, which depended on its activity of estrogenic or androgenic endocrine disruption.

According to a recent study, T may also play an important role in the anxiety-like behavior (Egashira et al., 2010). Due to disruptive effects of pubertal fenvalerate exposure on T synthesis (Zhang et al., 2009, 2010a,b), we further investigated whether pubertal fenvalerate exposure disrupts anxiety-related behaviors. We found that peripheral time was significantly increased in female mice treated with 30 mg/kg fenvalerate. By contrast, peripheral time was significantly decreased in the male mice treated with 7.5 mg/kg. These results are in agreement with others, in which developmental exposure to low-dose estrogenic endocrine disruptors (such as BPA or methoxychlor) altered sex differences in exploration and emotional responses (Gioiosa et al., 2007). Moreover, a recent study demonstrated that maternal BPA exposure increased "anxiety-like" behavior and resulted in the loss of exploration attitude in female offspring, but not in males (Poimenova et al., 2010). These data suggest that developmental exposure to EDC, such as BPA, methoxychlor and fenvalerate, increase anxiety activities in females.

Numerous data have demonstrated that steroid hormone (such as T or E_2) in the developing brain plays an important role in cognitive function and behavioral development (Paus et al., 2010; Spiteri et al., 2010; McCarthy, 2008). Firstly, T or E_2 in the developing brain might influence spatial learning and memory performance. According to an earlier report, a positive correlation was observed between T and spatial learning and memory performance in adult male white-footed mice (Pyter et al., 2006). Secondly, T or E_2 in the developing brain might influence aggressive behavior in males. According to a recent study, aromatization of T into E_2 is important for the development of aggressive behavior (Wu et al., 2009). Recently, we found that pubertal fenvalerate exposure disrupted T and E_2 synthesis in cerebral cortex. In addition, pubertal fenvalerate exposure disrupted the expression of AR in cerebral cortex (Liu et al., 2011). These results suggest that fenvalerate-induced impairment on cognition and behavioral development might be associated with its endocrine disruption on the developing brain.

In summary, the present study found that pubertal fenvalerate exposure impaired spatial cognition and memory in a gender-specific manner, that is, the impairment for spatial learning and memory is more serious in fenvalerate-exposed female mice than in male mice. In addition, pubertal fenvalerate exposure inhibited aggressive behavior in males. Moreover, pubertal fenvalerate exposure increases anxiety activities in females. These findings identify fenvalerate as candidate environmental risk factors for cognitive and behavioral development, especially in the critical period of development.

Conflict of interest

None.

Acknowledgments

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