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Effect of ketamine on exploratory behaviour in BALB/C and C57BL/6 mice

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ABSTRACT

In this study, we evaluated the effect of ketamine on exploratory locomotion behaviours in the Balb/c and C57BL/6 strains of mice, which differ in their locomotion behaviours.

Intraperitoneal administration of ketamine at three different doses (1, 5 or 10 mg/kg, 0.1 ml/10 gr body weight) was performed on adult male Balb/c and C57BL/6 mice. The same volume of saline was applied to the control group. The open-field and elevated plus maze apparatus were used to evaluate exploratory locomotion.

In the open-field test, Balb/c mice less spend time in the centre of the field and was decreased locomotor activity compared to C57BL/6 mice ($p<0.01$). Ketamine treatment of Balb/c mice at 10 mg/kg dose caused an increase in locomotor activity and an increase in the amount of time spent in the centre in the open-field test, compared to the control group ($p<0.05$). In C57BL/6 mice, ketamine treatment (1 and 10 mg/kg) decreased locomotor activity ($p<0.05$). In C57BL/6 mice, the three different doses of ketamine application each caused a decrease in the frequency of centre crossing ($p<0.001$) and the spent time in the centre ($p<0.05$).

In the elevated plus maze, the number of open-arm entries, the percentage of open-arm time and total arm entries were decreased in Balb/c mice compared to C57BL/6 mice ($p<0.001$). Ketamine treatment of Balb/c mice at 10 mg/kg dose caused an increase in the open-arm activity ($p<0.001$). Ketamine application (10 mg/kg) decreased the open-arm activity in C57BL/6 mice ($p<0.05$).

A subanaesthetic dose of ketamine increased exploratory locomotion in Balb/c mice. In contrast, a subanaesthetic dose of ketamine decreased exploratory locomotion in C57BL/6 mice. In conclusion, hereditary factors may play an important role in ketamine-induced responses.

1. Introduction

The non-competitive receptor antagonist ketamine has been used in paediatric and adult patients as a short-term dissociative anaesthetic agent since the 1960s (Annetta et al., 2005). Ketamine application causes behavioural and neurochemical effects in humans and experimental animals (Dunn et al., 1989; Krystal et al., 1994; Lindefors et al., 1997; Silvestre et al., 1997; Babar et al., 2001; Zarate et al., 2006). In clinical and experimental studies, subanaesthetic doses of ketamine affected to locomotor behaviours (Imre et al., 2006; Mandryk et al., 2005). Previous studies suggest that ketamine can act through NMDA receptors as well as the serotonergic, dopimanergic and noradrenergic systems (Lannes et al., 1991; Lindefors et al., 1997; Duncan et al., 1998). It has been suggested that ketamine-induced locomotor behaviour may connected with all above systems.

NMDA receptor antagonists can affect local dopamine and serotonin receptors by indirectly regulating cortical GABA release in mice (Lindefors et al., 1997). Low doses of ketamine, phencyclidine and MK-801-like NMDA receptor antagonists have been shown to increase the level of extracellular dopamine in the prefrontal cortex (Hondo et al., 1994; Verma and Moghaddam, 1996) and in the extracellular 5-HIAA level of the frontal cortex (Löscher and Hönack, 1992). A decrease in the level of glutamic acid decarboxylase mRNA has been observed following MK-801 application, along with a decrease in GABA synthesis (Laprade and Soghomonian, 1995).

Rodents naturally experience fear and anxiety when exposed to a novel open field, which causes a behavioural response (Dolu and Özemsi, 2004; Bourin et al., 2007). The open field test has been used to evaluate locomotor activity and anxiety. Different strains of mice show different anxiety and locomotion responses in open-field tests (Carola et al., 2002; Tang et al., 2002). Balb/c mice have been found to exhibit decreased exploratory behaviours compared to C57BL/6 mice in an open-field test (Tang et al., 2002).

The elevated plus maze, has been extensively used in rodents as a test of fear, anxiety and exploratory behaviour (Lister, 1987; Benattia et al., 2011; Moreira et al., 2007). Previous research has shown that differences exist between exploratory and anxiety-like behaviours in the elevated plus maze of C57BL/6 and BALB/c. For example,

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some investigators have reported that Balb/c mice show higher levels of anxiety-like behaviours and lower of exploratory behaviours in the elevated plus maze than C57BL/6 mice (An et al., 2011). In addition to environmental factors, some studies have explored the genetic component of these effects and suggest that anxiety levels might be hereditary (Cle'ment et al., 2002).

In this study, we evaluated the effects of an NMDA receptor antagonist, using different subanaesthetic doses of ketamine (1 mg/kg, 5 mg/kg or 10 mg/kg), on exploratory locomotion in different strains of mice (Balb/c and C57BL/6).

2. Materials and methods

The experimental protocols were confirmed by the Local Ethics Committee of the Çukurova University Medical Sciences Experimental Search and Application Center. The procedures in the study were in accordance with the NIH Guide for Care and Use of Animals.

2.1. Animals

In this study, two different strains of mice (Balb/c and C57BL/6) were used and were bred in the Çukurova University Faculty of Medicine Physiology Laboratory. Adult (8–10 week-old) male mice (body weight 31.8 ± 0.4 for Balb/c mice, 29.2 ± 0.4 for C57BL/6 mice) were used for behavioural tests. Food and water were given without restriction. The room temperature was fixed at 21 ± 2 °C, and behavioural tests were performed at this temperature. Animals were housed in a room with a 12-hour light/dark cycle ($05^{:00}$–$17^{:00}$ light, $17^{:00}$–$05^{:00}$ dark). Behavioural tests were performed between $9^{:00}$–$12^{:00}$. Hand and room adaptations were applied to animals before behavioural tests were performed.

2.2. Ketamine treatment

Ketamine hydrochloride (Ketasol, Richter Pharma AG, 100 mg/ml) diluted in saline (% 0.9 NaCl) was applied to mice via intraperitoneum injection at doses of 1 mg/kg, 5 mg/kg and 10 mg/kg (at a volume/body weight ratio of 0.1 ml/10 gr) 15 min before behavioural testing. The same volume of saline was injected into the control group.

2.3. Apparatus

2.3.1. Open-field

The open-field apparatus used in the behavioural tests measured 60 × 60 × 24, which was made of black plexiglass, had an open top and a base that was divided into thirty-six squares and was enclosed by a 1 cm thick wall, forming a square box. The squares next to the wall were designated as “peripheral” and the others were designated as “centre.” Peripheral fields are safe and protected, whereas the centre field is nonprotective in the open-field apparatus. In open-field experiments, exploratory locomotor activity were measured using the following criteria: the distance travelled in the centre and peripheral fields, spending time in the centre versus the peripheral field, frequency of centre crossing, latency of entering the centre and frequency of defecation (Carola et al., 2002; Kinsey et al., 2007; Prut and Belzung, 2003). The frequency of rearing (vertical activity) was evaluated as well (Prut and Belzung, 2003). For the open-field test, mice were treated with ketamine or saline 15 min before the test and were placed anywhere in the apparatus. Behaviours were recorded for ten minutes using a video camera. The open-field apparatus was illuminated by 165 lx.

2.3.2. Elevated plus maze

The elevated plus maze consisted of two perpendicular open arms (30 cm × 5 cm) and two closed arms (30 cm × 5 cm × 15 cm) also in perpendicular position. The open and closed arms were connected by a central platform (5 cm × 5 cm). The maze was made of black plexiglass and was 40 cm above the floor. After treatment, the animal was placed at the centre of the plus-maze facing the enclosed arm, and observed for 5 min. In the elevated plus maze, exploratory locomotor activity were evaluated. The elevated plus maze was illuminated by 165 lx (the open arms). A video camera was used to monitor the animal's behaviour. The maze apparatus was cleaned after each trial. The following parameters were registered: number of entries in the open arm, total entries (open and closed arm) and time of permanence in the open arm. The percentage of time spent in the open arms was calculated. The animals were randomly ordered for testing. The person scoring the behaviour was blind to the treatment (Carola et al., 2002).

2.4. Statistics

Data values are expressed as mean ± S.E. For statistical analyses of strain versus drug interaction, two-way ANOVA was applied using the SPSS 11.5 computer programme. One-way ANOVA followed by the Tukey HSD test was used for comparisons between the groups. The Kruskal–Wallis test was applied to determine the normal distribution or variance of groups that were not homogenic. The Mann–Whitney-U test was applied for comparisons within the group. Significance levels were set at $p<0.05$.

3. Results

3.1. Open-field test

In the open-field test, the time spent in the centre and periphery of the apparatus, a two-way ANOVA-significant strain effect [$F(1,73)=5$ $p<0.05$)] and a strain × drug interaction were confirmed [$F(1,73)=34.02$ $p<0.001$)], whereas a drug effect was not confirmed [$F(1,73)=0.7$ $p>0.05$)]. The time spent in the centre of the apparatus was decreased in Balb/c mice compared to C57BL/6 mice, with a corresponding increase in the time spent in the periphery ($p<0.001$). In Balb/c mice, treatment with 5 mg/kg and 10 mg/kg doses of ketamine caused an increase in the time spent in the centre and a decrease in the time spent in the periphery compared to control animals ($p<0.05$). In C57BL/6 mice, application of 1 mg/kg, 5 mg/kg and 10 mg/kg doses ketamine caused a decrease in the time spent in the

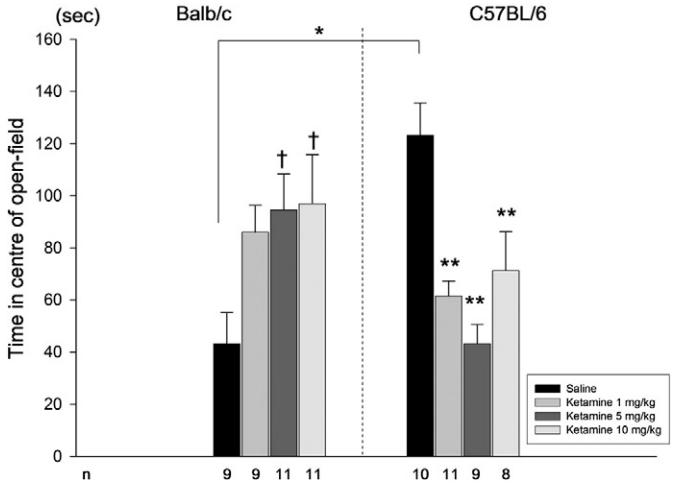

Fig. 1. Time in the centre of the open field (s). Data are expressed as mean ± SE. **$p<0.05$, *$p<0.001$ compared to saline-treated C57BL/6 mice and †$p<0.05$ compared to saline-treated Balb/c mice. Statistical analysis included a one-way ANOVA analysis followed by the Tukey HSD test.

centre of the apparatus and an increase in the time spent in the periphery ($p<0.05$) (Fig. 1).

Distance travelled on the apparatus, there was a significant strain effect [$F(1,73)=12.2$ $p<0.05$)] and strain × drug interaction [$F(1,73)=17.8$ $p<0.05$)], whereas there was no drug effect [$F(1,73)=1.2$ $p>0.05$)]. Distance travelled was decreased in Balb/c mice compared to C57BL/6 mice ($p<0.05$). In Balb/c mice, the 10 mg/kg dose of ketamine caused an increase in distance travelled compared to the control group and the 5 mg/kg dose ($p<0.05$). In C57BL/6 mice, the three different doses of ketamine application each caused a decrease in the distance travelled on the apparatus ($p<0.05$). There was no difference in the distance travelled on the apparatus between the groups receiving 1 mg/kg, 5 mg/kg or 10 mg/kg ketamine (Fig. 2).

For the frequency of centre crossing, a significant strain effect [$F(1,73)=13.5$ $p<0.05$)] and strain × drug interaction were confirmed [$F(1,73)=34.5$ $p<0.05$)], whereas a drug effect was not confirmed [$F(1,73)=1.8$ $p>0.05$)]. In the frequency of centre crossing was decreased in Balb/c mice compared to C57BL/6 mice ($p<0.001$). In Balb/c mice, all three doses of ketamine caused an increase in the frequency of centre crossing ($p<0.05$). In C57BL/6 mice, the three different doses of ketamine application each caused a decrease in the frequency of centre crossing ($p<0.001$). There was no difference in the frequency of centre crossing between the groups receiving 1 mg/kg, 5 mg/kg or 10 mg/kg ketamine (Fig. 3).

For frequency of rearing, a significant strain effect [$F(1,73)=44$ $p<0.05$)], drug effect [$F(1,73)=4.8$ $p<0.05$)] and strain × drug interaction were confirmed [$F(1,73)=12.7$ $p<0.05$)], using two-way ANOVA analysis. There was decreased in the frequency of rearing in Balb/c mice compared to C57BL/6 mice ($p<0.001$)] (Fig. 4). There was no difference in the frequency of rearing (vertical activity) between Balb/c mice receiving the three different doses of ketamine ($p>0.05$)]. In C57BL/6 mice was decreased in vertical activity by ketamine application at all doses (1 mg/kg and 5 mg/kg ketamine $p<0.05$, 10 mg/kg ketamine $p<0.001$). Furthermore, the 10 mg/kg dose of ketamine caused a decrease in vertical activity compared to the 5 mg/kg dose of ketamine ($p<0.05$) (Fig. 4).

For frequency of defecation, a strain effect [$F(1,73)=0.01$ $p>0.05$)], a drug effect [$F(1,73)=0.08$ $p>0.05$)] and a strain × drug interaction were not confirmed [$F(1,73)=1.7$ $p>0.05$)]. A significant difference was not observed for latency in of entering the centre, using the Kruskal–Wallis test [$H(7, N=77)=7.4$ $p>0.05$] (Table 1).

The position Figs. 1, 2, 3 and 4, and Table 1.

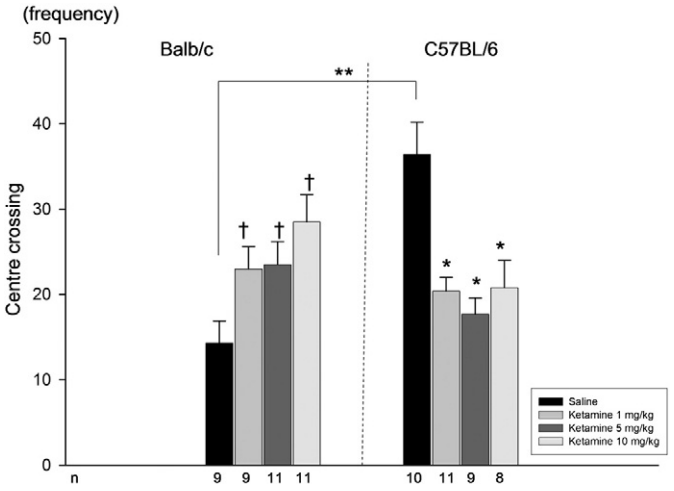

Fig. 3. The frequency of centre crossing in the open-field test. Data are expressed as mean ± SE. **$p<0.05$, *$p<0.001$ compared to saline-treated C57BL/6 mice and †$p<0.05$ compared to saline-treated Balb/c mice. Statistical analysis included a one-way ANOVA analysis followed by the Tukey HSD test.

3.2. Elevated plus maze

In the elevated plus maze, groups differed significantly in terms of both the number of open-arm entries [$H(7, N=68)=30.3$ $p<0.001$], the percentage of open-arm time [$H(7, N=68)=30.7$ $p<0.001$] and total arm entries [$H(7, N=68)=24.8$ $p<0.01$]. In the number of open-arm entries ($U=2$ $p<0.001$), the percentage of open-arm time ($U=0$ $p<0.001$) and total arm entries ($U=1$ $p<0.001$) were decreased in Balb/c mice compared to C57BL/6 mice. In Balb/c mice, the number of open-arm entries (control $U=3$ $p<0.001$, 1 mg/kg ketamine $U=5$ $p<0.05$), the percentage of open-arm time (control $U=1.5$ $p<0.001$, 1 mg/kg ketamine $U=8$ $p<0.05$) and total arm entries (control $U=0$ $p<0.001$, 1 mg/kg ketamine $U=10.5$ $p<0.05$) were increased 10 mg/kg ketamine compared to groups of control and 1 mg/kg ketamine. In Balb/c mice, the 10 mg/kg dose of ketamine caused an increase in the number of open-arm entries ($U=22.5$ $p<0.05$), the percentage of open-arm time ($U=15$ $p<0.05$) compared to group of the 5 mg/kg ketamine. In Balb/c mice, treatment with 5 mg/kg doses of ketamine caused a significant increase in the

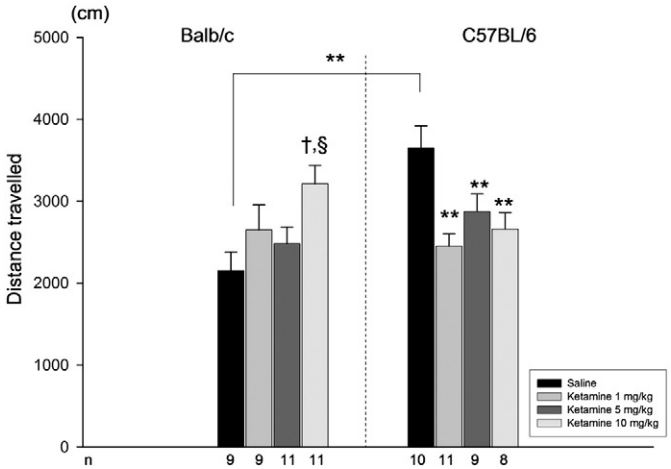

Fig. 2. Distance travelled in the open-field test (cm). Data are expressed as mean ± SE. **$p<0.05$ compared to saline-treated C57BL/6 mice, †$p<0.05$ compared to saline-treated Balb/c mice and §$p<0.05$ compared to ketamine (5 mg/kg) Balb/c mice. Statistical analysis included a one-way ANOVA analysis followed by the Tukey HSD test.

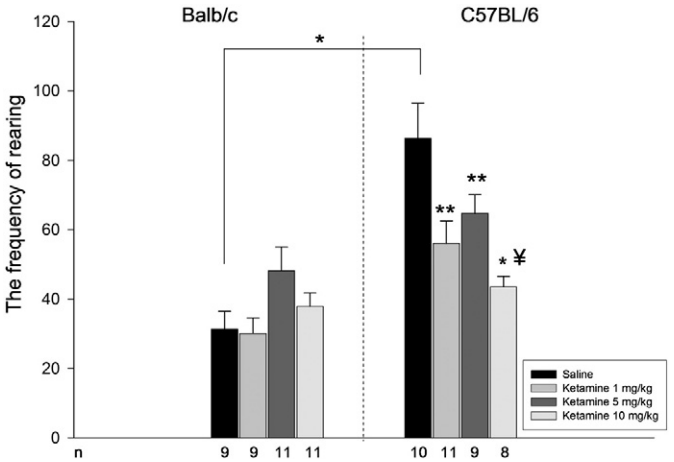

Fig. 4. The frequency of rearing in the open-field test. Data are expressed as mean ± SE. **$p<0.05$, *$p<0.001$ compared to saline-treated C57BL/6 mice and ¥$p<0.05$ compared to ketamine (5 mg/kg) C57BL/6 mice. Statistical analysis included a one-way ANOVA analysis followed by the Tukey HSD test.

Table 1
Latency of entering the centre and frequency of defecation in the open field.

	Mice	Control	Ket 1 mg/kg	Ket 5 mg/kg	Ket 10 mg/kg
Centre latency	Balb/c	31.2 ± 12	25.1 ± 6.3	26.7 ± 5.9	12.5 ± 2.5
	C57BL/6	26.6 ± 6.4	34.7 ± 7	45.6 ± 13	36.6 ± 12.2
Defecation	Balb/c	2.4 ± 0.5	2.2 ± 0.4	3.2 ± 0.3	3.5 ± 1
	C57BL/6	3.2 ± 0.7	2.4 ± 0.5	2.3 ± 0.5	2.2 ± 0.8

Data are expressed as mean ± SE. Ket: Ketamine.

number of open-arm entries (U = 16 $p<0.05$) and total arm entries (U = 7.5 $p<0.05$) compared to group of control. Furthermore, the 1 mg/kg doses of ketamine caused a significant increase in total arm entries compared to group of control (U = 12 $p<0.05$) (Figs. 5, 6, 7).

In C57BL/6 mice, the number of open-arm entries (U = 39.5 $p<0.05$), the percentage of open-arm time (U = 3 $p<0.05$) and total arm entries (U = 18.5 $p<0.05$) were decreased in the 10 mg/kg ketamine compared to groups of control. Treatment with 10 mg/kg doses of ketamine caused a significant decrease in the percentage of open-arm time (U = 9.5 $p<0.05$) compared to group of 1 mg/kg ketamine and in the number of open-arm entries (U = 13.5 $p<0.05$) compared to group of 5 mg/kg ketamine. There was not significant difference in the number of open-arm entries, the percentage of open-arm time and total arm entries in group of 5 mg/kg ketamine compared to group of control. There was decreased in the number of open-arm entries in group of 1 mg/kg ketamine compared to group of control (U = 6 $p<0.05$)(Figs. 5, 6, 7).

The position Figs. 5, 6, and 7.

4. Discussion

In two different strains of mice, the exploratory locomotion was evaluated by the open-field test and elevated plus maze. We also found that C57BL/6 mice had an increase in exploratory locomotion and rearing behaviour in the open-field test compared to Balb/c mice. In other studies were reported that in C57BL/6 mice increased horizontal and vertical locomotor activity, which is compatible with our findings (Carola et al., 2002; Tang et al., 2002). Consistent with previous studies, C57BL/6 mice spent more time in the centre of the open field and in the open arm of elevated plus maze (Augustsson and Meyerson, 2004; Crawley et al., 1997; Tang et al., 2002). The defecation shows the activation of the autonomic nervous system (Denenberg, 1969; Gorman et al., 2000). A decrease in the frequency of defecation with increased locomotor activity was shown in previous studies (DeFries et al., 1978; Flint et al., 1995). In spite of the difference in locomotor activity, we found no difference in the frequency of defecation. These results suggest that Balb/c mice have lower exploratory behaviours than C57BL/6 mice, which have a lower level of basal locomotor activity. This supports the hypothesis that genetic factors have important effects on novelty adaptation.

In Balb/c mice, 10 mg/kg subanaesthetic dose of ketamine caused an increase in the time spent in the centre of the open field and in the time spent in the open arm of elevated plus maze. Consistent with our findings, subanaesthetic doses of ketamine were shown to increase horizontal locomotor activity in rodents in an open-field test (Imre et al., 2006; Mandryk et al., 2005). Similar to other reports,

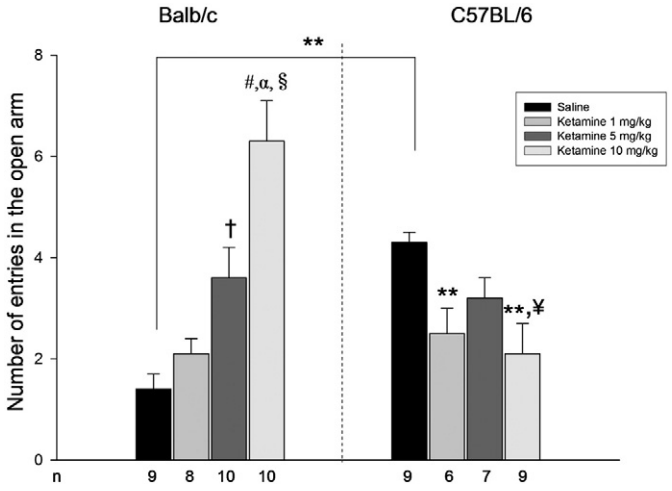

Fig. 6. Number of entries in the open arm in the elevated plus maze. Data are expressed as mean ± SE. **$p<0.05$, compared to saline-treated C57BL/6 mice, ¥$p<0.05$ compared to ketamine (5 mg/kg) C57BL/6 mice, †$p<0.05$, #$p<0.001$ compared to saline-treated Balb/c mice, α$p<0.05$ compared to ketamine (1 mg/kg) Balb/c mice, §$p<0.05$ compared to ketamine (5 mg/kg) Balb/c mice. Statistical analysis included Kruskal–Wallis test followed by the Mann–Whitney U test.

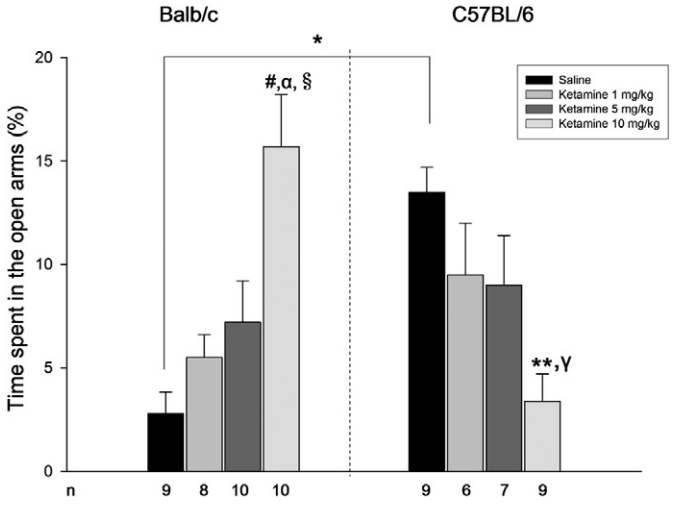

Fig. 5. Time spent in the open arms (%) in the elevated plus maze. Data are expressed as mean ± SE. **$p<0.05$, *$p<0.001$ compared to saline-treated C57BL/6 mice, γ$p<0.05$ compared to ketamine (1 mg/kg) C57BL/6 mice, #$p<0.001$ compared to saline-treated Balb/c mice, α$p<0.05$ compared to ketamine (1 mg/kg) Balb/c mice, §$p<0.05$ compared to ketamine (5 mg/kg) Balb/c mice. Statistical analysis included Kruskal–Wallis test followed by the Mann–Whitney U test.

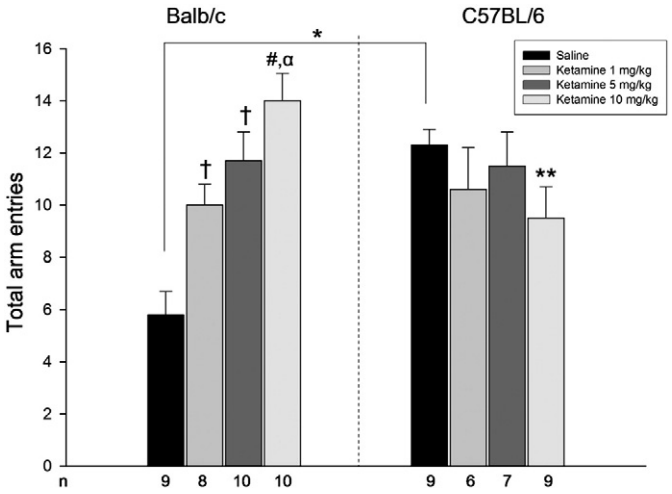

Fig. 7. Total arm entries (open and closed arm) in the elevated plus maze. Data are expressed as mean ± SE. **$p<0.05$, *$p<0.001$ compared to saline-treated C57BL/6 mice, †$p<0.05$, #$p<0.001$ compared to saline-treated Balb/c mice, α$p<0.05$ compared to ketamine (1 mg/kg) Balb/c mice. Statistical analysis included Kruskal–Wallis test followed by the Mann–Whitney U test.

the different doses of ketamine had no affect on vertical behaviour or frequency of defecation in Balb/c mice (Garcia et al., 2008; Silvestre et al., 1997). Several preclinical studies have demonstrated that NMDA antagonists, such as MK-801, AP7 and others, locomotor activity increased in rats injected into distinct brain areas (Garcia et al., 2008; Kos et al., 2006a; Menard and Treit, 2000). In Balb/c mice, the increase in exploratory locomotor behaviours by the three different doses of ketamine might be due to NMDA receptor blockage of ketamine. In addition to NMDA receptors, the increase in locomotor activity could be caused by effects on the dopaminergic system (Duncan et al., 1998; Laprade and Soghomonian, 1995; Löscher and Hönack, 1992). Consistent with this idea, ketamine showed an increase in locomotor activity, which is what would be expected from a dopaminergic agonist (Yamamoto et al., 1997).

In the open-field test, three different doses of ketamine caused a decrease in locomotor and vertical activity in C57BL/6 mice. Kos et al. (2006b) reported a decrease in locomotor activity and vertical activity by subanaesthetic doses of ketamine application in C57BL/6 mice. Ketamine application caused a decrease in exploratory behaviours in this strain, which have a high basal locomotor activity. In other reports, ketamine was shown to have an exploratory behaviours increase in most strains of mice studied (da Silva et al., 2010; Imre et al., 2006). However, different exploratory behaviour effects by ketamine application have been seen in different apparatuses, depending on the strain of mice (Silvestre et al., 1997). A decrease in locomotor activity in C57BL/6 mice by NMDA receptor blockage is believed to be due to the activation of noradrenergic and serotonergic neurons (Hayase et al., 2006). In previous studies, they found significant alterations associated with strain in the maturation of the dopaminergic and serotonergic systems in these two strains (C57BL/6 and Balb/c) (Yochuma et al., 2010). Regional differences of neurochemical systems can explain the behavioural differences in two strains that is shown by ketamine treatment.

5. Conclusion

In this study, different doses of ketamine application had different effects in different strains of mice. In the open field test, Balb/c mice showed an increase in exploratory locomotion by ketamine application. C57BL/6 mice, ketamine application caused a decrease in locomotor activity. The differential effect of ketamine on exploratory locomotion in the different strains could be due to an effect of NMDA receptors or on several other important neurotransmitter systems, including serotonergic, dopaminergic, noradrenergic and opiate receptors. These results suggest that hereditary factors may play an important role in the influence of ketamine on behaviour.

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