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D_2 and D_4 Receptors Involved in Methamphetamine and *p*-Chloroamphetamine-induced Amnesia in the Step-through Passive Avoidance Test in Mice

Yi-Kuei Wong[1], Hui-Hung Wang[4], Ming-Kuan Chou[1], Jiin-Cherng Yen[1], Li-Kang Ho[1], Shi-Kwang Lin[2], Yuh-Chiang Shen[3,5,6], Jyh-Fei Liao*[1]

1. Department and Institute of Pharmacology, School of Medicine, National Yang-Ming University, Taipei 11221, Taiwan;
2. Taipei City Pschiatric Center, Taipei City Hospital, Taipei, Taiwan;
3. National Research Institute of Chinese Medicine, Taipei, Taiwan;
4. Institute of BioMedical Science, Academia Sinica;
5. Institute of Biomedical Sciences, National Chung-Hsing University, Taichung, Taiwan;
6. National Taipei University of Nursing and Health Science.

ABSTRACT

Dopamine D_2 and D_4 receptors play an important role in cognitive functions. Acute administration of both methamphetamine and *p*-chloroamphetamine induced amnesia in animals but mechanisms of action remained unclear. The aim of this study was to exam both D_2 and D_4 receptor activation involved in methamphetamine and *p*-chloroamphetamine induced amnesia. Dopamine D_2 and D_4 receptor antagonists were challenged proceeding of acute administration of methamphetamine or *p*-chloroamphetamine in a passive avoidance test, an amnesia murine model. Acute administration of methamphetamine (3 mg/kg, i.p.) before the training trial induced cognition impairment in passive avoidance test. The amnesic effect could be ameliorated by pretreatment of haloperidol (a dopamine D2 receptor antagonist) and L-745,870 (a dopamine D4 antagonist). Methamphetamine also induced locomotor hyperactivity that was improved by pretreatment of haloperdiol but not by L-745,870. *p*-Chloroamphetamine (5 mg/kg, i.p.) also induced amnesia in passive avoidance test which was significant attenuated by haloperidol, eticlopride (a selective D_2 antagonist) and L-745,870 when these antagonists were administrated 50 min before the training trial or immediately after the training trial. We proposed that both D_2 and D_4 receptors activation were participated in impairment of memory acquisition induced by methamphetamine and *p*-chloroamphetamine while dopamine D_2 receptors activation was also involved in locomotor hyperactivity induced by methamphetamine.

Keywords: *p*-Chloroamphetamine. Methamphetamine. Haloperidol. L-745,870. Amnesia. Passive avoidance test

*Corresponding Author Email: yuhcs@nricm.edu.tw
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INTRODUCTION

Methamphetamine, an analogue of amphetamine, is a widely abused psychostimulant which causes a numerous psychosocial, neuropsychiatric, and medical problems[1]. Applying toxic methamphetamine administration schedule by three injections of 10 mg/kg, i.p. at 2-h intervals depleted dopamine and serotonin in striatum and impaired object recognition task in male rats[2]. Administration of methamphetamine by three injections of 5 mg/kg, i.p. at 2-h intervals to mice decreased striatal tyrosine hydroxylase with impairment of consolidation of learned place preference, and this impairment was not improved by dopamine D_1 or D_2 receptor agonists[3]. Acute pretreatment of amphetamine (1 and 3 mg/kg, i.p.) significantly increased the percentage time in the aversive enclosed arm in the plus-maze discriminative avoidance task and the authors reported that amphetamine had an amnestic effect that can be attenuated by tacrine, a cholinesterase inhibitor[4]. Furthermore, sulpiride, a dopamine D_2 receptor antagonist, significantly improved concussive brain injury-induced impairments in learning and memory, indicating that activation of dopaminergic neuronal function is involved in the concussive brain injury-induced amnesia[5]. Previously, we also showed that acute administration methamphetamine induced amnesia in mice and this effect could be ameliorated by a selective D_2 receptor antagonist eticolpride[6]. However, the mechanisms of action involved in acute administration of methamphetamine or amphetamine on various memory performances are still controversy. Dopamine is an important neurotransmitter in the brain and plays a key role in cognition function and motor control[7]. Dopamine receptors are divided into two pharmacological subtypes, namely D_1-like and D_2-like receptors, which typically couple to Gs and Gi protein and trigger to increase or decrease adenylyl cyclase activity respectively[8]. The D_2-like receptors including D_2, D_3, and D_4 receptors are potent targets for neurolpetic drugs[9]. The distribution of D_2 receptors were detected in striatum and accumbens nucleus and prefrontal cortex in rats[10], [11]. Previously study showed that co-perfusion D_2-like receptor agnoist quinpirole and NMDA into nucleus accumbens attenuated NMDA-induced acetylcholine (ACh) release in prefrontal cortex and this effect was blocked by D_2 antagonist haloperidol in rats[12]. D_4 receptors were widely distributed in the hippocampus, frontal cortex, entorhinal cortex, caudate putamen, nucleus accumbens in rat[13]. Although D_2 receptor in memory is still controversy, bilateral microinjection of D_3 receptor antagonist S33084 into the prefrontal cortex of rats improvement in social novelty discrimination and novel object recognition but bilateral microinjection of D_2 receptor antagonist L741,626 into the prefrontal cortex (but not striatum) impairment novel object recognition[14].

Furthermore, D_2 and D_4 receptor mRNA co-localization expressed in monkey prefrontal cortex[15]. The low dose of dopamine D_4 receptor antagonist PUN-101387G had been reported to attenuate working impairment induced by the inverse benzodiazepine agonist FG7142 in monkey[16]. However, the role of D_4 receptor antagonist in cognition is unclear. *p*-Chloroamphetamine, a derivative of amphetamine, is relatively potent than amphetamine in the induction of serotonin, dopamine and norepinephrine release[17]. *p*-Chloroamphetamine induced animal locomotor hyperactivity, decreased investigatory behavior[18], and impaired learning and memory in passive avoidance test[19]. The deficiency in avoidance learning by *p*-chloroamphetamine was attributed to enormous central serotonin release stimulated by *p*-chloroamphetamine which, in turn, impaired animal passive avoidance performance via multiple serotonin subtype receptors[20]. It is well-known that central cholinergic function plays an important role in mediating the process of learning and memory. *p*-Chloroamphetamine blocked the memory-enhancing effect of physostigmine in rats with NMDA-induced unilateral lesions of the nucleus basalis of Meynert in passive avoidance test[21]. Furthermore, exposure to multiple doses of methamphetamine and *p*-chloroamphetamine impaired passive avoidance performance and resulted in significant depletions of dopamine, serotonin, and their metabolites in several brain regions, especially in striatum[22]. It is still unknown the role of dopamine D_2 and D_4 receptor antagonists in *p*-chloroamphetamine-induced amnesia. Therefore, the objective of the present study was to exam the effect of acute administration of methamphetamine as well as *p*-chloroamphetamine in memory performance of step-though passive avoidance tasks and evaluate the effects of dopamine D_2 and D_4 receptor antagonists in methamphetamine- and *p*-chloroamphetamine-induced impairments in memory performance and locomotor activity in mice.

MATERIALS AND METHODS

Animals

Male Institute of Cancer Research (ICR) mice (25-30 g) were obtained from the Animal Center of National Taiwan University. They were maintained on a 12-h light and 12-h dark cycle (light on between 7:00 and 19:00) with food and tap water *ad libitum*. All experimental protocols in this study comply with international guidelines and were approved by Institutional Animal Care and Use committee (IACUC) of National Yang-Ming University.

Drugs

Methamphetamine hydrocholoride (methamphetamine) was purchased from National Bureau of Controlled Drugs, Department of Health, R.O.C. (Taiwan); haloperidol hydrochloride, (S)-

eticlopride hydrochloride, L-745,870 trihydrochloride were purchased from Tocris (Ellisville, USA); *p*-chloroamphetamine hydrochloride were purchased from Sigma-Aldrich Chemical Co. (St. Louis, USA). The drugs were dissolved in twice-filtered water and i.p. administrated in a dosage of 0.1 ml per 10 g of body weight. The dosage of the test drug was administrated according to the published literature.

Step-through passive avoidance test

The experimental procedure was performed according to our previous established method[23]. The experimental apparatus for the step-through passive avoidance test is an automated shuttle-box (Cat. 7551 Passive Avoidance Controller and Cat. 7553 Passive Avoidance Mouse Cage, UGO Basile, Italy), which is divided into an illuminated compartment and a dark compartment of the same size by a wall with a guillotine door. Each mouse was put through the adaptation trial by placing it gently in the illuminated compartment, facing away from the dark compartment. After 10 s, the door was opened and the mouse moved into the dark compartment freely. When the latency to leave the illuminated compartment was less than 30 s, the mouse was chosen for the training trial 2 h later. The training trial is similar to the adaptation trial except that the door is closed as soon as the mouse steps into the dark compartment and an inescapable foot shock (0.6 mA, 2 s) is delivered through the grid floor. The retention test was performed 24 h after the training trial in the similar manner without the electric shock and the step-through latency to the dark compartment was recorded. The maximal cut-off time for step-through latency was 300 s.

Locomotor activity test

Locomotor activity was measured in a multi-box ActiMot detection system (TSE, Germany). This system uses individual photocell activity units (48 X 48 cm) connected to a control unit. Each unit consisted of a base frame with two pairs of 32 light-barrier strips (transmitter and receiver), set at a distance of 14 mm, which are sensitive to infrared light, and thus animal locomotor activity was measured. An additional pair of light-barrier strips (Z-coordinate) was used to detect rearing activity. Data for the number and sequence of photocell interruptions were collected on a computer. After vehicle or drug treatment, each mouse was transported from the home cage to the activity cage and allowed to acclimate for a minimum of 1 min before testing began and the locomotor activity was measured for 25 min. Total distance was presented as the locomotor activity.

Experimental design

In methamphetamine-induced amnesia model, methamphetamine (1-10 mg/kg, i.p.) was administrated 30 min before the or immediately after the training trial and D_2 or D_4 receptor

antagonist was administrated 40 min before the training trial. In *p*-chloroamphetamine-induced amnesia model, *p*-chloroamphetamine was administrated 30 min before the training trial to induced amnesia. D_2 or D_4 receptor antagonists were administrated 50 min before the training trial or immediately after the training trial to exam the memory acquisition and consolidation, respectively.

Data analysis

The results of passive avoidance test were expressed as medians, interquartile ranges and the 5th to 95th percentile ranges, and the data were analyzed by Kruskal-Wallis non-parametric one way analysis of variance (ANOVA) on ranks and followed by Mann-Whitney rank sum test. The results in locomotor activity were expressed as means $\pm$ S.E.M. and the data were analyzed using one way ANOVA and followed by Student-Newman-Keuls test. The statistical significance level was set at $p < 0.05$.

RESULTS AND DISCUSSIONS

Effects of Methamphetamine and p-Chloroamphetamine on the Memory Performance in Native Mice

None of drug treatment had significant effect on either the step-through latency in the training trial or the sensitivity to electric shocks throughout the passive avoidance test compared with the control group (data not shown). Methamphetamine (3, 5, 10 mg/kg, i.p.) administrated 30 min before the training trial impaired performance in the retention test ($H(4) = 23.704$, $p < 0.01$) as shown in table 1, but no significant effect in methamphetamine 1 mg/kg (compared with control, $p > 0.05$). *p*-Chloroamphetamine (1-7.5 mg/kg, i.p.) administrated 30 min before training trial dose dependently abolished mice performance in the retention test at 5 and 7.5 mg/kg i.p. as shown in table 2. This result was similar with previously report[22]. Therefore, methamphetamine and *p*-chloroamphetamine at the dose of 3 mg/kg, and 5 mg/kg respectively, were used in this study.

Effects of Dopamine D_2 or D_4 Receptor Antagonists on Methamphetamine-induced Amnesia and Changes of Locomotor Activity

To examine whether the activation of dopamine D_2 and D_4 receptors plays a role in methamphetamine-induced amnesia and changes of locomotor activity, D_2 antagonist was pretreated before methamphetamine administration. As shown in Fig. 1a, either pre-training or post-training administration of methamphetamine (3 mg/kg, i.p.) induced amnesia in the passive avoidance test and pretreatment with haloperidol (0.25 mg/kg, i.p.) attenuated

methamphetamine-induced amrnesia (Kruskal–Wallis ANOVA, $H(5) = 37.526$, $p < 0.001$). In addition, pretreatment with L-785,870 (0.03 mg/kg, i.p.), a selective D_4 antagonist, also attenuated methamphetamine-induced amnesia (Kruskal–Wallis ANOVA, $H(5) = 39.124$, $p < 0.001$) in Figure 1c. As shown in Figure 1b, when the locomotor activity was measured soon after the training trial, pre-training or post-training administration of methamphetamine (3 mg/kg, i.p.) markedly increased the locomotor activity in mice, whereas pretreatment with haloperidol (0.25 mg/kg, i.p.) itself markedly decreased the basal locomotor activity and also significantly inhibited methamphetamine-induced increase in locomotor activity ($F_{(5,54)} = 56.169$, $p < 0.001$). However, pretreatment with L-785,870 (0.03 mg/kg, i.p.) itself had neither significant effect on basal locomotor activity or on methamphetamine-induced increase in locomotor activity ($F_{(5,59)} = 18.887$, $p > 0.05$, compared with methamphetamine groups) (Figure 1d).

Table 1: Effect of methamphetamine administrated 30 min before the training trial on the step-through latency in the training trial and the retention test of the step-through avoidance test in mice

Treatment (mg/kg, i.p.)	N	Median of latency (interquartile range, sec)	
		Training trial	Retention test
Control	10	9.6 (7.0-11.6)	265.9 (135.2-298.0)
methamphetamine 1.0 mg/kg	20	8.7 (6.8-18.7)	116.6 (55.4-180.6)
methamphetamine 3.0 mg/kg	11	5.5 (4.1-13.1)	43.9 (23.9-115.3)*
methamphetamine 5.0 mg/kg	19	6.2 (4.5-7.6)	49.8 (13.1-283.3)*
methamphetamine 10.0 mg/kg	15	7.2 (4.5-9.0)	19.3 (13.8-35.3)*
		H(4) = 9.257	H(4) = 23.704
		$P > 0.05$	$P < 0.01$

* $p<0.05$, as compared with the control group by the Kruskal-Wallis one way analysis of variance on ranks

Table 2: Effect of *p*-chloroamphetamine administrated 30 min before the training trial on the step-through latency in the training trial and the retention test of the step-through avoidance test in mice

Treatment (mg/kg, i.p.)	N	Median of latency (interquartile range, sec)	
		Training trial	Retention test
Control	20	8.3 (5.7-11.9)	300 (77.0-300.)
p-chloroamphetamine 1.0 mg/kg	9	6.0 (3.8-8.8)	207.5 (21.8-288.8)
p-chloroamphetamine 2.5 mg/kg	8	6.0 (4.9-14.7)	211.0 (42.3-300)
p-chloroamphetamine 5.0 mg/kg	2	6.5 (5.2-7.9)	25.2 (13.9-53.5)*
p-chloroamphetamine 7.5 mg/kg	3	5.4 (3.6-9.4)	18.5 (9.9-27.9)*
		H(4) = 5.9	H(4) = 27.3
		$P > 0.05$	$P < 0.01$

* $p<0.05$, as compared with the control group by the Mann-Whitney U test

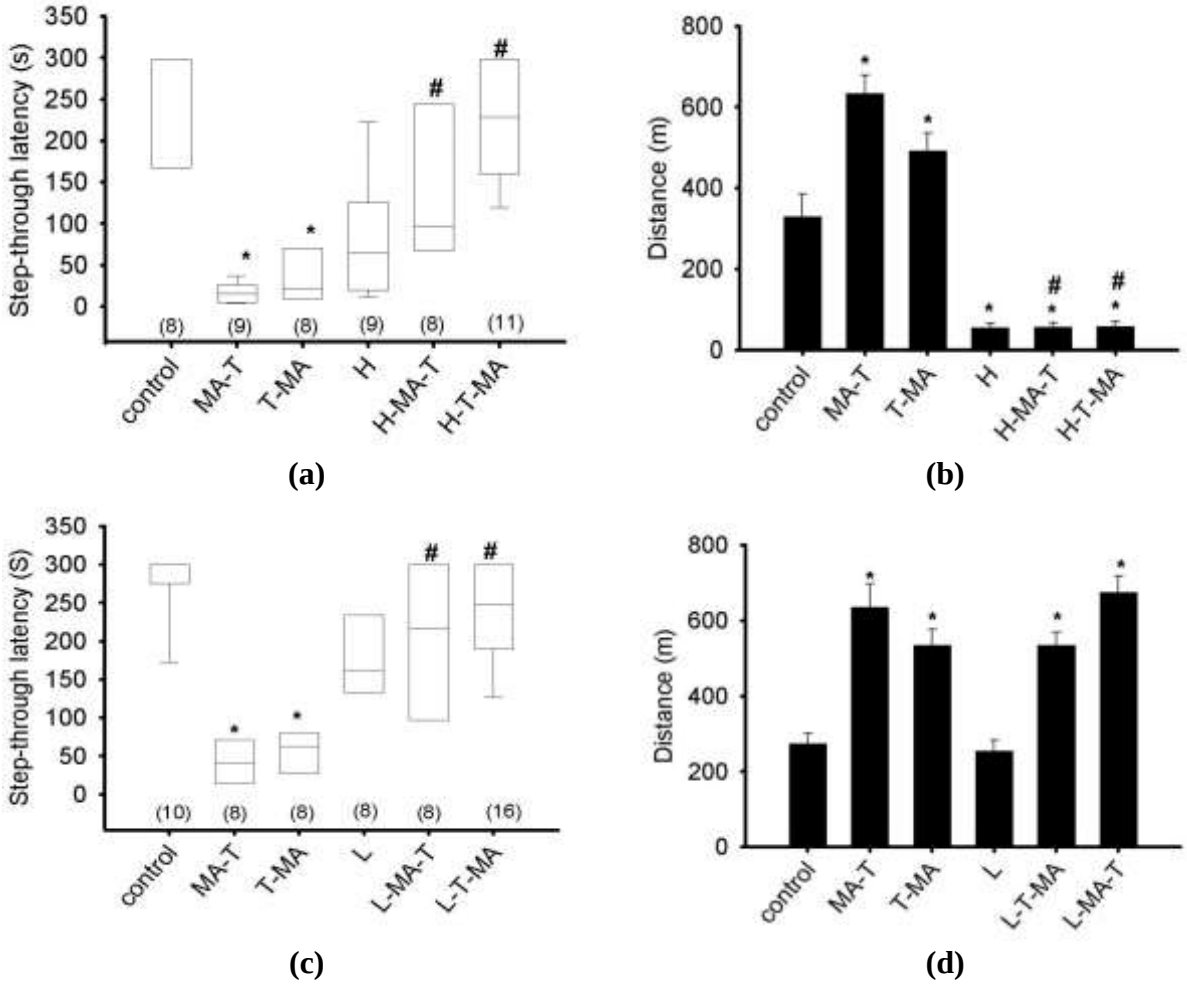
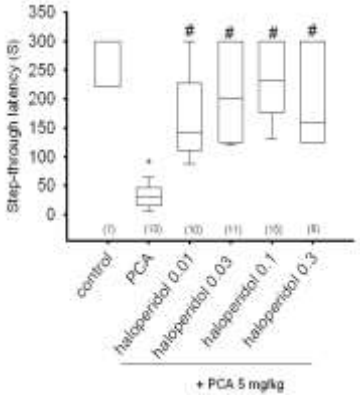


Figure 1: Effects of dopamine D_2-like receptor antagonists on methamphetamine-induced amnesia and changes of locomotor activity in mice. Haloperidol (H, 0.25 mg/kg, i.p.), or L745,870 (L, 0.03 mg/kg, i.p.) was administered 40 min before the training trial and methamphetamine (3 mg/kg, i.p.) was administered either 30 min before the training trial (MA-T) or immediately after the training trial (T-MA). The locomotor activity was measured for 25 min immediately after the training trial. The locomotor activity was expressed as movement distance (m). (a) and (c): Effect of dopamine D2-like receptor antagonists haloperidol or L745, 870 on methamphetamine-induced amnesia in the step-through passive avoidance test, respectively. The step-through latency was recorded in the retention test performed 24 h after the training trial. Data are expressed as medians (horizontal bar within the column), inter-quartile range (column), and the 5^{th} to 95^{th} percentile ranges. The number of mice in each group is indicated in parentheses. (b) and (d): Effect of haloperidol or L745, 870 on methamphetamine-induced increase in the locomotor activity, respectively. In (b) and (d), data are expressed as mean ± S.E.M. and analyzed by one way ANOVA and followed by Student-Newman-Keuls test. $^{*}P < 0.05$, as compared with the control group; $^{\#}P < 0.05$, as compared with the corresponding MA-T or T-MA group.

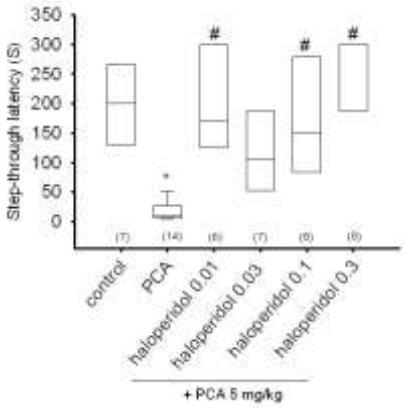
Effects of Dopamine D_2 or D_4 Receptor Antagonists on p-Chloroamphetamine-induced Amnesia and Changes of Locomotor Activity

To test whether the activation of dopamine D_2 and D_4 receptors plays a role in *p*-chloroamphetamine-induced amnesia, D_2 or D_4 antagonists was pretreated before *p*-chloroamphetamine administration. Haloperidol (0.01-0.3 mg/kg, i.p.) significantly improved *p*-chloroamphetamine-induce*d* amnesia when administrated before the training trial (Kruskal–Wallis ANOVA, $H(5) = 35.734$, $P < 0.001$) (Figure 2a) and immediately after the training trial (Kruskal–Wallis ANOVA, $H(5) = 34.643$, $P < 0.001$) (Figure 2b) with significant doses at 0.1 and 0.3 mg/kg. On the other hand, eticlopride (0.01-0.1 mg/kg, i.p.) also showed remarkable effects in improving animal retention performance when administrated before the training trial (Kruskal–Wallis ANOVA, $H(4) = 19.925$, $P < 0.001$) (Figure 2c) and immediately after the training trial (Kruskal–Wallis ANOVA, $H(4) = 37.7$, $P < 0.001$) (Fig. 2d) with significant doses at 0.1 mg/kg. On the profile of D_4 receptor, the results showed that L-745,870 obviously attenuated *p*-chloroamphetamine-induce*d* amnesia when administrated before the training trial (Kruskal–Wallis ANOVA, $H(5) = 43.844$, $P < 0.001$) (Figure 2e) with the significant doses at 0.003 and 0.01 mg/kg, and immediately after the training trial (Kruskal–Wallis ANOVA, $H(5) = 28.306$, $p< 0.001$) (Figure 2f) with significant doses at 0.003 and 0.1 mg/kg. However, L-785,870 (0.01 – 1 mg/kg, i.p.) and *p*-chloroamphetamine (3 mg/kg) either itself or combined had no significant effects on basal locomotor activity ($F_{(7,114)} = 0.769$, $p = 0.615$, data not shown). Mesolimbocortical dopamine plays a role in learning and memory. Pre-test intra-dorsal hippocampal injection dopamine D_1 (SCH23390) and D_2 (sulpiride) receptor antagonist reversed hepatic encephalopathy-indcued amnesia in passive avoidance test in mice[25]. Post-training administrated $GABA_A$ receptor muscimol into the ventral tegmental area (VTA) was significantly inhibited memory retrieval in passive avoidance in rats and this effect was ameliorated by administration of sulpiride in CA1 area of the hippocampus, but not SCH23390 [26]. In addition, it was reported that activation of D_2 receptors impaired passive avoidance learning and locomotion and a non-selective D_2 receptor antagonist, pimozide, enhanced the acquisition of the passive avoidance response in mice[27, 28]. Furthermore, it was reported that pre-training but not post-training administration of amphetamine induced amnesic action on the plus-maze discriminative avoidance task in mice[4] and acute administration of methamphtamine caused doapmine release in rats[29]. Consistance with these data, the present study demonstrated that acute methamphetamine-induced amnesia may involve the over-activation of dopamine D_2 and D_4 receptors, because a nonselective D_2 receptor antagonist (haloperidol) and a selective D_4

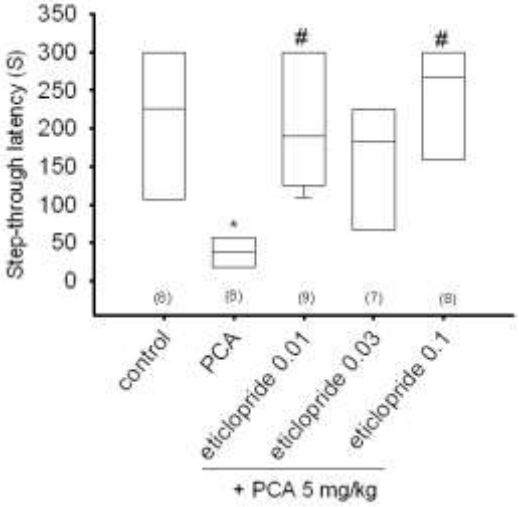
receptor antagonist (L-785,870) could attenuate memory impairment induced by pre-training or post-training administration of methamphetamine. However, previously study showed that both methamphetamine and amphetamine produce a broad of spectrum of pharmacological and behavioral effects depending on pattern of administration and dosing[30]. Our previously results showed that acute or repeated administration of methamphetamine both induced amnesia and D_2 receptor antagonist eticlopride improved acute but not repeated administration of methamphetamine-induced amnesia in mice[6]. Our previously also study also showed that balicalein, a kind of flavonoids with free radical scavenging action[31], had effective in binge but not acute administration of methamphetamine-induced amnesia and hyper-locomotor activity[6]. In terms of locomotor activity, both amphetamine and methamphetamine were equipotent in activating the locomotor activity in rats[31], and amphetamine-induced hyperactivity was antagonized by D_2 receptor antagonists[33]. Present study showed that pre-training or post-training administration of methamphetamine (3 mg/kg, i.p.) induced amnesia and hyper-locomotion in mice and these effects were alleviated by haloperidol. L-785,870 also attenuated methamphetamine-induced amnesia but not hyper-locomotion in mice. Administration of dopamine D_2 receptor agonist, quinpirole, led to dose-dependent increase of locomotion while D_2 receptor antagonist sulpiride decreased locomotor activity[34]. In contrast to the classical neuroleptic, haloperidol, and the atypical neuroleptic, clozapine, the selective dopamine D_4 receptor antagonist L-745,870 failed to antagonize amphetamine-induced hyperactivity in mice[35]. These results also suggested that methamphetamine-induced amnesia is independent from its effect on locomotor activity. To examine the effects of dopamine D_2 and D_4 receptors antagonists in memory, this study also evaluated amphetamine analogous, *p*-chloroamphetamine in memory performance. In this study, we showed that *p*-chloroamphetamine-induced amnesia in a dose-dependent manner and *p*-chloroamphetamine-induced amnesia was successfully inhibited by D_2 receptor antagonists haloperidol (0.1–0.3 mg/kg, i.p.) and eticlopride (0.1 mg/kg, i.p.) when administrated 50 min before and immediately after the training trial. Furthermore, comparable profile of the attenuation effects were also seen in treatment with selective D_4 receptor antagonist L-745,870 at both pre- (0.003, 0.01 mg/kg, i.p.) and post-training (0.003, 0.1 mg/kg, i.p.) administration in mice. However, post-training administration of L-745,870 (0.003, 0.1 mg/kg, i.p.) alleviated *p*-chloroamphetamine-induced amnesia in U-shape dose manner and this result implied that *p*-chloroamphetamine-induced amnesia might mediate multiple mechanism. In conclusion, the present study demonstrated that administration of methamphetamine and *p*-chloroamphetamine induced memory impairment in the step-through



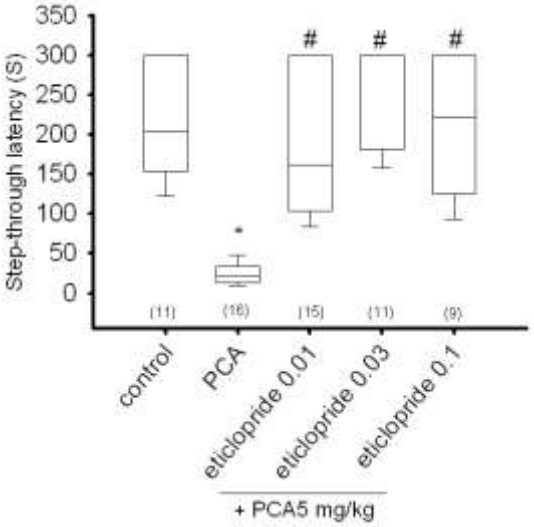
(a). Pre-training administration



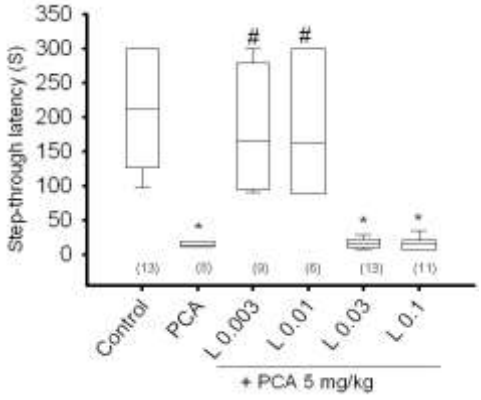
(b). Post-training administration



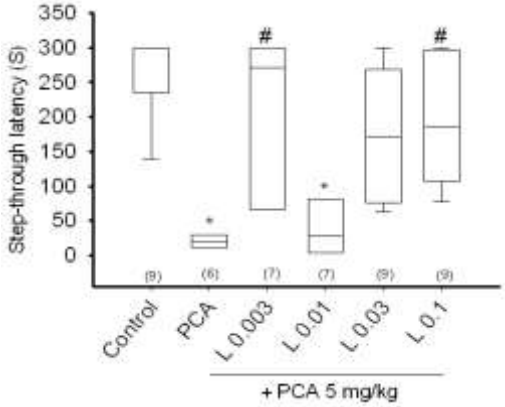
(c). Pre-training administration



(d). Post-training administration



(e). Pre-training administration



(f). Post-training administration

Figure 2: Effects of dopamine D_2-like receptor antagonists on *p*-chloroamphetamine-induced amnesia in the set-through passive avoidance. *p*-Chloroamphetamine (5 mg/kg, i.p.) was administrated 30 min before the training trial to induced amnesia. Various doses of haloperidol (0.01-0.3 mg/kg, i.p.), eticlopride (0.01-0.1 mg/kg, i.p.) and L-745,870 (0.03-0.1 mg/kg, i.p.) were administrated 50 min before the training trial as shown in (a), (c), and (e), or immediately after the training trial as shown in (b), (d), (e). * *P*<0.05, as compared with the control group; $^{\#}$*P*<0.05, as compared with the corresponding *p*-Chloroamphetamine group.

passive avoidance test in ICR mice, mainly *via* the over-activation of D_2 and D_4 receptors. D_2 and D_4 receptor antagonists both attenuated methamphetamine and *p*-chloroamphetamine induced memory impairment in passive avoidance. This amnesic effect of methamphetamine could be differentiated from its stimulatory effect on locomotor activity. These results implied that methamphetamine-induced amnesia and hyper-locomotion may mediate different signal pathway.

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Disclosure Statement

The authors declare that there are no conflicts of interest.

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