

## Research Article

# Unusual Effects of Nicotine as a Psychostimulant on Ambulatory Activity in Mice

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The present study examined the effect of nicotine, alone and in combination with various drugs that act on the CNS, on ambulatory activity, a behavioral index for locomotion, in ICR (CD-1) strain mice. Nicotine at 0.25–2 mg/kg acutely reduced ambulatory activity of ICR mice. The effect of nicotine was similar to that of haloperidol and fluphenazine but distinct from that of bupropion and methylphenidate. ICR mice developed tolerance against the inhibitory effect of nicotine on ambulatory activity when nicotine was repeatedly administered. This effect was also distinct from bupropion and methylphenidate as they produced augmentation of their ambulation-stimulating effects in ICR mice. Nicotine reduced the ambulation-stimulating effects of bupropion and methylphenidate as well as haloperidol and fluphenazine. Taken together, nicotine exhibited unusual effects as a psychostimulant on ambulatory activity in ICR mice.

## 1. Introduction

Nicotine (NIC), the primary psychoactive substance in tobacco smoke, produces a variety of psychoactive effects and has been believed to be a type of psychostimulant. In humans, NIC produces convulsions, tremors, and excitation of respiration [1], elevates the arousal level [2, 3], facilitates behaviors and performance [4–6], and improves cognition and attention abilities [7–10]. These effects support the idea that NIC is a type of psychostimulant. On the other hand, other studies suggest that NIC may have depressant and/or sedative effects [11–14]. In addition, it is well known that prolonged use of typical psychostimulants such as amphetamine, methamphetamine, and cocaine causes schizophrenia-like mental abnormalities (amphetamine (or methamphetamine) psychosis, and cocaine psychosis) [15–21] whereas prolonged smoking has been known not to produce schizophrenia-like psychosis. In contrast, smoking has been proposed as a form of self-medication to alleviate symptoms of schizophrenia [22–28]. The self-medication hypothesis arose from the following observations: (1) patients with schizophrenia frequently smoke cigarettes at a two- to four-fold higher rate than that seen in the general population;

(2) patients with schizophrenia smoke heavier than the normal population [29–35]; (3) patients with schizophrenia extract more nicotine from each cigarette than other smokers [36]. Thus, smoking may ameliorate symptoms of schizophrenia, and the NIC in cigarettes could contribute to the heavy smoking that has been noted in patients with schizophrenia. If the self-medication hypothesis for NIC in patients with schizophrenia is true, the effect of NIC in patients with schizophrenia is in striking contrast to the effects of typical psychostimulants in these patients as typical psychostimulants usually worsen schizophrenia or produce schizophrenia-like psychosis.

In animals, locomotion is a fundamental behavioral index for evaluating the stimulating effects of psychostimulants. Typical psychostimulants such as amphetamine [37–42], methamphetamine [43–50], and cocaine [49, 51–56] consistently stimulate locomotion in rats and mice. In terms of rodent locomotion, NIC may exhibit different properties from those of typical psychostimulants. NIC usually stimulates locomotion in rats to a small degree but frequently fails to produce locomotor hyperactivity in mice [57–66]. Although genetic factors could be involved in species and/or strain differences for effects of NIC on locomotion in rodents

[67], the effects of NIC on rodent locomotion should largely depend on pharmacological properties of NIC, as typical psychostimulants consistently stimulate locomotion in any species and/or strains of rodents. The effects of NIC on locomotion in rodents are still controversial.

Ambulatory activity is a kind of locomotor activity for mice and can be measured using a tilt-type ambulometer [68]. Because effects of many kinds of psychoactive drugs have been evaluated using this method [69–88], using ambulatory activity as a behavioral index has been well established. The present study examined the effect of NIC, alone and in combination with various CNS acting drugs, on ambulatory activity in ICR (or CD-1) strain mice, which is one of the popular strains for general multipurpose use.

## 2. Materials and Methods

**2.1. Animals.** Male ICR (CD-1) strain mice (Clea Japan, Tokyo, Japan) aged 7–10 weeks and weighing between 35 and 42 g were housed in aluminum cages (3 mice/cage) with a stainless-steel mesh top and paper bedding. Commercial solid food (Clea Japan) and tap water were available *ad libitum*. Cages were placed in a room artificially illuminated by fluorescent lamps on a 12L:12D schedule (light period: 07:00–19:00), at a room temperature of  $25 \pm 1^\circ\text{C}$ .

All experiments were conducted in accordance with the guidelines of the Ethics Committee for Experimental Animals of the National Institute for Environmental Studies, Japan.

**2.2. Drugs.** NIC was purchased from Nacalai Tesque (Kyoto, Japan). Psychostimulants bupropion (BUP) and methylphenidate (MP; Ritalin) were purchased from Sigma-Aldrich (Tokyo, Japan) and Japan Ciba-Geigy (Hyogo), respectively. CNS depressants fluphenazine (FLU), haloperidol (HAL), and nAChR antagonist mecamlamine (MECA) were purchased from Sigma-Aldrich. NIC, BUP, MP, FLU, and MECA were dissolved in saline (0.9% NaCl, Nacalai Tesque). HAL was dissolved in 0.1% acetic acid solution (Wako Pure Chemicals, Osaka, Japan).

**2.3. Measurement of Ambulatory Activity in ICR Mice.** Ambulatory activity was measured using a tilt-type ambulometer consisting of 10 bucket-like Plexiglas activity cages (20 cm in diameter) (SAM-10; O'Hara and Co., Tokyo, Japan) ([68, 89, 90], in press (DOI: 10.1016/j.ntt.2011.08.007), [91–93]). Each activity cage is sustained by a fulcrum in the center of the bottom of the cage; the fulcrum tilts according to horizontal movement of the mouse in the activity cage. The tilting movement of the activity cage activates microswitches that surround the cage. The number of activations of microswitches during a set time is recorded, and the result is printed.

## 3. Experimental Procedure

**Experiment 1.** Effect of a single subcutaneous administration of NIC on ambulatory activity in ICR mice.

ICR mice were placed individually in activity cages, and, after 30 min of adaptation, saline or 0.25, 0.5, 1, or 2 mg/kg of NIC was administered subcutaneously. Thereafter, ambulatory activity was continuously measured for 60 min.

**Experiment 2.** Effects of single subcutaneous administrations of BUP, MP, HAL, or FLU on ambulatory activity in ICR mice.

After 30 min of adaptation in the activity cages, saline or 5 or 10 mg/kg of BUP, 2 or 4 mg/kg of MP, 0.031, 0.0625, or 0.125 mg/kg of HAL, or 0.625, 0.125, or 0.25 mg/kg of FLU was subcutaneously administered to ICR mice. Thereafter, ambulatory activity was continuously measured for 60 min.

**Experiment 3.** Effect of repeated administrations of NIC, BUP, or MP on ambulatory activity.

After 30 min of adaptation in the activity cages, saline or 1 mg/kg of NIC, 10 mg/kg of BUP, or 4 mg/kg of MP was administered to mice, and ambulatory activity was measured for 60 min. These steps were repeated on the same mice 5 times with 3- to 4-day intervals and changes of effects of these drugs on ambulatory activity were examined.

**Experiment 4.** Interaction between NIC and MECA on ambulatory activity.

After 30 min of adaptation in the activity cages, saline or 1 mg/kg of MECA was subcutaneously administered to mice. Ten minutes later, saline or 2 mg/kg of NIC was subcutaneously administered to the mice, followed by measurements of ambulatory activity for 60 min.

**Experiment 5.** Interactions between BUP and HAL or FLU or between NIC and BUP or MP on ambulatory activity.

After 30 min of adaptation in the activity cages, saline or 0.031, 0.0625, or 0.125 mg/kg of HAL or 0.0625, 0.125, or 0.25 mg/kg of FLU was subcutaneously administered to mice. Ten minutes later, saline or 10 mg/kg of BUP was subcutaneously administered to the mice, followed by measurements of ambulatory activity for 60 min.

After 30 min of adaptation in the activity cages, saline or 0.25, 0.5, 1, or 2 mg/kg of NIC and saline, 10 mg/kg of BUP, or 4 mg/kg of MP were subcutaneously coadministered to mice, followed by measurements of ambulatory activity for 60 min.

**3.1. Statistical Analysis.** To eliminate differences of baseline ambulatory activity, the activity of each animal after administration of each drug was normalized using the total activity of the animal during the 30 min adaptation period before administration of each drug.

The time course of ambulatory activity after single administration of NIC was initially examined using repeated-measures analysis of variance (ANOVA). Then, differences at each time point were examined using one-way ANOVA, followed by Dunnett's test. Differences in total ambulatory activity over 1 h were analyzed using one-way ANOVA, followed by Dunnett's test.  $P < 0.05$  was established as the level of significance.

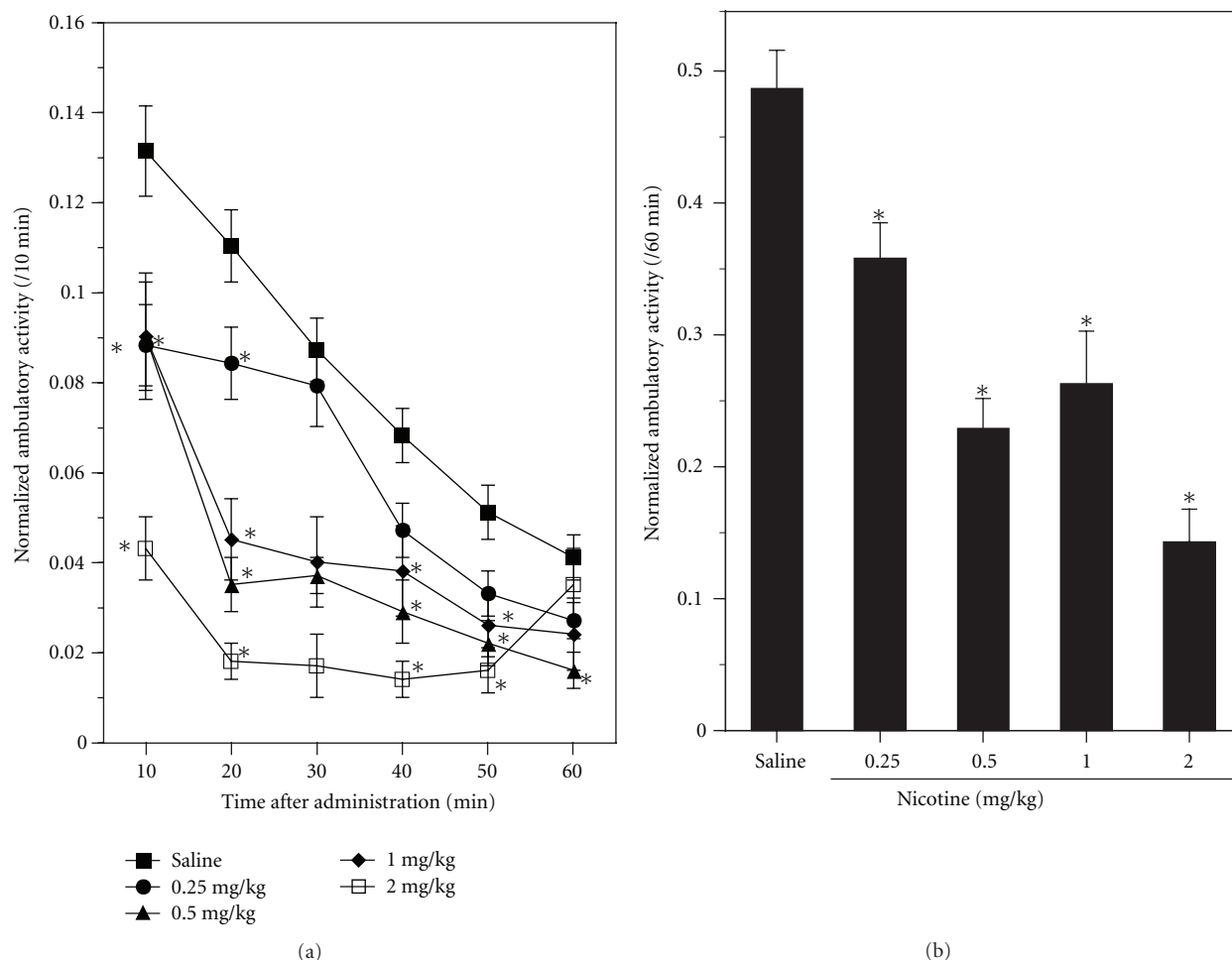


FIGURE 1: Ambulatory activity in ICR mice after single subcutaneous administration of saline or 0.25–2 mg/kg of NIC. The figure shows normalized ambulatory activity that was obtained by normalizing the actual ambulatory measurement using total ambulatory activity during the 30 min adaptation period before administration to each mouse. (a) Time courses of ambulatory activity after subcutaneous administration of saline or 0.25–2 mg/kg of NIC. Symbols represent mean values of ambulatory activity for 10 min periods, and vertical lines indicate standard error of the mean (SEM).  $N = 40$ – $100$  animals per dose group. (b) Total ambulatory activity over 60 min after administration of saline or various doses of NIC. Filled columns indicate mean values of total ambulatory activity for 60 min, and vertical lines indicate SEM. Data in Figure 1(a) were analyzed by repeated measures ANOVA, followed by one-way ANOVA and Dunnett's test.  $*P < 0.05$  compared with saline control at each time point. Data in Figure 1(b) were analyzed using one-way ANOVA, followed by Dunnett's test.  $*P < 0.05$  compared with saline control.

## 4. Results

**Experiment 1.** Effect of a single subcutaneous administration of NIC on ambulatory activity in ICR mice.

NIC at 0.25–2 mg/kg significantly reduced the ambulatory activity of ICR mice (Figures 1(a) and 1(b)). The effect of NIC was dose dependent (Figure 1(b);  $F(4, 275) = 20.1$ ,  $P < 0.05$ ) and lasted as long as 60 min—Figure 1(a); repeated measures ANOVA (dose:  $F(4, 275) = 20.1$ ,  $P < 0.05$ ; time:  $F(5, 1375) = 61.896$ ,  $P < 0.05$ ; interaction:  $F(20, 1375) = 5.582$ ,  $P < 0.05$ ).

**Experiment 2.** Effects of single subcutaneous administrations of BUP, MP, HAL, or FUL on ambulatory activity in ICR mice.

BUP at 5–10 mg/kg (Figure 2(a)) and MP at 2–4 mg/kg (Figure 2(b)) stimulated ambulatory activity of ICR mice in a dose-dependent manner (BUP:  $F(2, 217) = 26.132$ ,  $P < 0.05$ ; MP:  $F(2, 317) = 100.433$ ,  $P < 0.05$ ).

HAL at 0.031–0.125 mg/kg (Figure 2(c)) and FLU at 0.625–0.25 mg/kg (Figure 2(d)) significantly and dose-dependently reduced the ambulatory activity in ICR mice (HAL:  $F(3, 68) = 5.945$ ,  $P < 0.05$ ; FLU:  $F(3, 64) = 2.907$ ,  $P < 0.05$ ).

**Experiment 3.** Effect of repeated administrations of NIC, BUP, or MP on ambulatory activity.

Repeated administration of saline to the same mice with intervals of 3–4 days did not significantly alter normalized ambulatory activity of ICR mice (Figures 3(a), 3(b), and 3(c);  $F(4, 595) = 2.373$ ,  $P > 0.05$ ). The inhibitory effect of

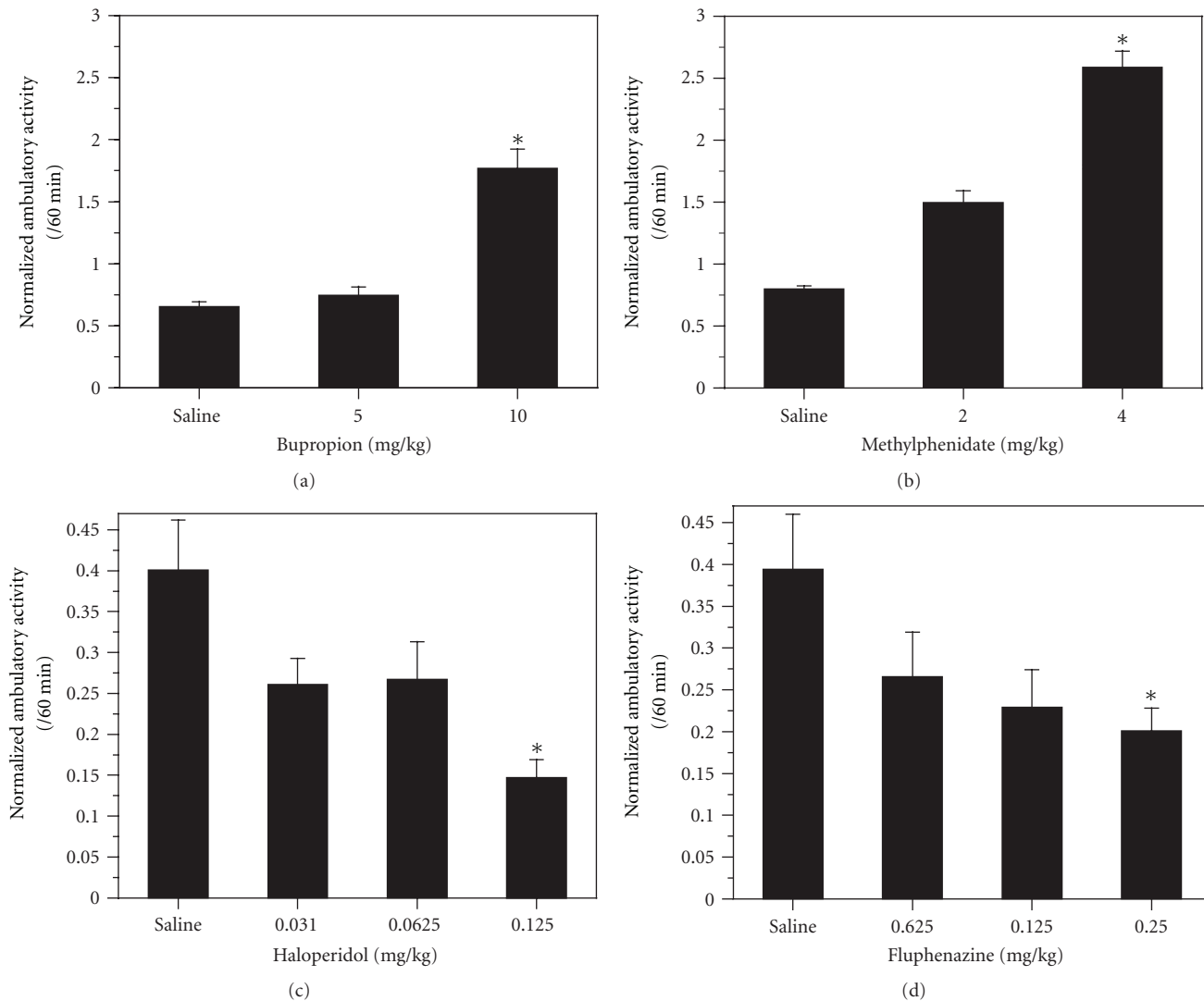


FIGURE 2: Effects of single subcutaneous administrations of 5–10 mg/kg of BUP (a), 2–4 mg/kg of MP (b), 0.031–0.125 mg/kg of HAL (c), or 0.625–0.25 mg/kg of FLU (d) on ambulatory activity in ICR mice. Results are shown using normalized values. Filled columns indicate mean values of total ambulatory activity for 60 min, and vertical lines indicate SEM. (a)  $N = 40$ –120, (b)  $N = 100$ –120, (c)  $N = 18$ , and (d)  $N = 16$ –18. \* $P < 0.05$  compared with saline control.

1 mg/kg of NIC on ambulatory activity gradually attenuated during repeated administration with intervals of 3–4 days (Figure 3(a)). Analysis of variance failed to show statistical significance on the change of effect of NIC ( $F(4, 95) = 2.433$ ,  $P = 0.0527$ ); however, significant differences between saline control and NIC observed at the first three administrations disappeared at the last two administrations, indicating that the inhibitory effect of NIC gradually weakened. The ambulation-stimulating effect of 10 mg/kg of BUP (Figure 3(b)) and 4 mg/kg of MP (Figure 3(c)) gradually and significantly increased when they were administered repeatedly to the same mice with intervals of 3–4 days (BUP:  $F(3, 236) = 4.942$ ,  $P < 0.05$ ; MP:  $F(4, 494) = 10.489$ ,  $P < 0.05$ ) (Figures 3(b) and 3(c)).

**Experiment 4.** Interaction between NIC and MECA on ambulatory activity.

NIC at 2 mg/kg significantly reduced the ambulatory activity and 1 mg/kg of MECA eliminated the inhibitory effect of 2 mg/kg of NIC on ambulatory activity when administered together (Figure 4;  $F(2, 137) = 5.598$ ,  $P < 0.05$ ).

**Experiment 5.** Interactions between BUP and HAL or FLU between NIC and BUP or MP on ambulatory activity.

HAL at 0.031–0.125 mg/kg (Figure 5(a)) and 0.0625–0.25 mg/kg of FLU (Figure 5 (b)) significantly reduced the ambulation-stimulating effect of 10 mg/kg of BUP in a dose-dependent manner (HAL:  $F(4, 115) = 21.148$ ,  $P < 0.05$ ; FLU:  $F(4, 185) = 15.622$ ,  $P < 0.05$ ). Similarly, 0.25–2 mg/kg of NIC significantly reduced the ambulation-stimulating effect of 10 mg/kg of BUP in a dose-dependent manner (Figure 5(c);  $F(5, 234) = 23.778$ ,  $P < 0.05$ ). The same doses of NIC also significantly reduced the ambulation-stimulating

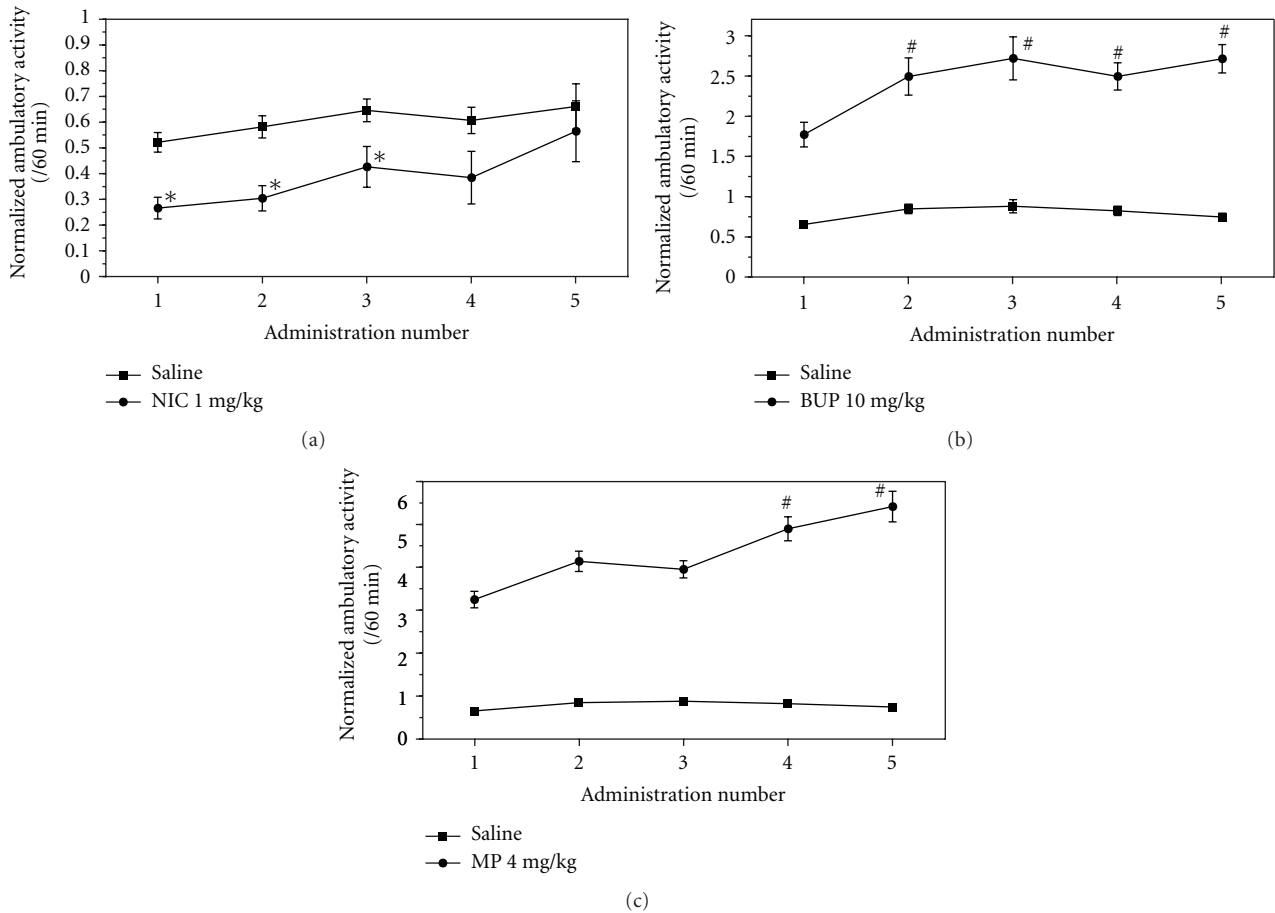


FIGURE 3: Effects of repeated administrations of saline or 1 mg/kg of NIC (a), 10 mg/kg of BUP (b), or 4 mg/kg of MP (c) to the same ICR mice on ambulatory activity. The administration was repeated 5 times with intervals of 3-4 days. Symbols represent mean values of ambulatory activity for 60 min periods after the administrations, and vertical lines indicate SEM. Saline:  $N = 60$ , NIC:  $N = 20$ , BUP:  $N = 60$ , and MP:  $N = 100$ . \* $P < 0.05$  compared with saline control at the same time point. # $P < 0.05$  compared with the first administration of the drug.

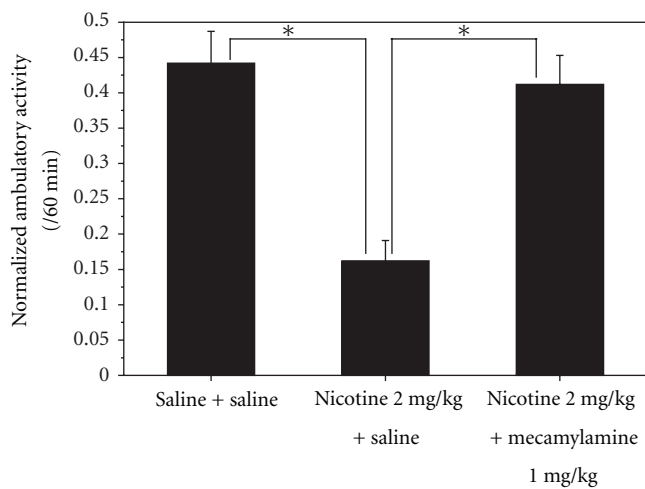


FIGURE 4: Effects of combined administration of 2 mg/kg of NIC with 1 mg/kg of MECA on ambulatory activity. Filled columns indicate mean values of total ambulatory activity for 60 min after the administrations, and vertical lines indicate SEM. Saline + saline:  $N = 80$ , NIC + saline:  $N = 20$ , and NIC + MECA:  $N = 40$ . \* $P < 0.05$  compared with NIC + saline.

effect of 4 mg/kg of MP (Figure 5(d);  $F(5, 194) = 23.86$ ,  $P < 0.05$ ).

### 5. Discussion

Ambulatory activity measured using a tilt-type amburometer is sensitive to vertical movement of mice in the activity cage of the amburometer but insensitive to vertical movement of animals. Therefore, ambulatory activity can be used as a measure of behavioral indices for locomotion in mice. This notion is further supported by results of the previous [91–93] and present studies that show the ambulatory activity of ICR (CD-1) mice was stimulated by psychostimulants such as BUP and MP, which have been known to stimulate mouse locomotion [94–99], and reduced by depressants such as HAL and FLU, which have been known to reduce mouse locomotion [98, 100–102].

The present study revealed that NIC at 0.25–2 mg/kg acutely reduced ambulatory activity in ICR mice under the same experimental condition for evaluating effects of psychostimulants BUP and MP and depressants HAL and FLU. Psychostimulants sometimes cause stereotyped or repetitive

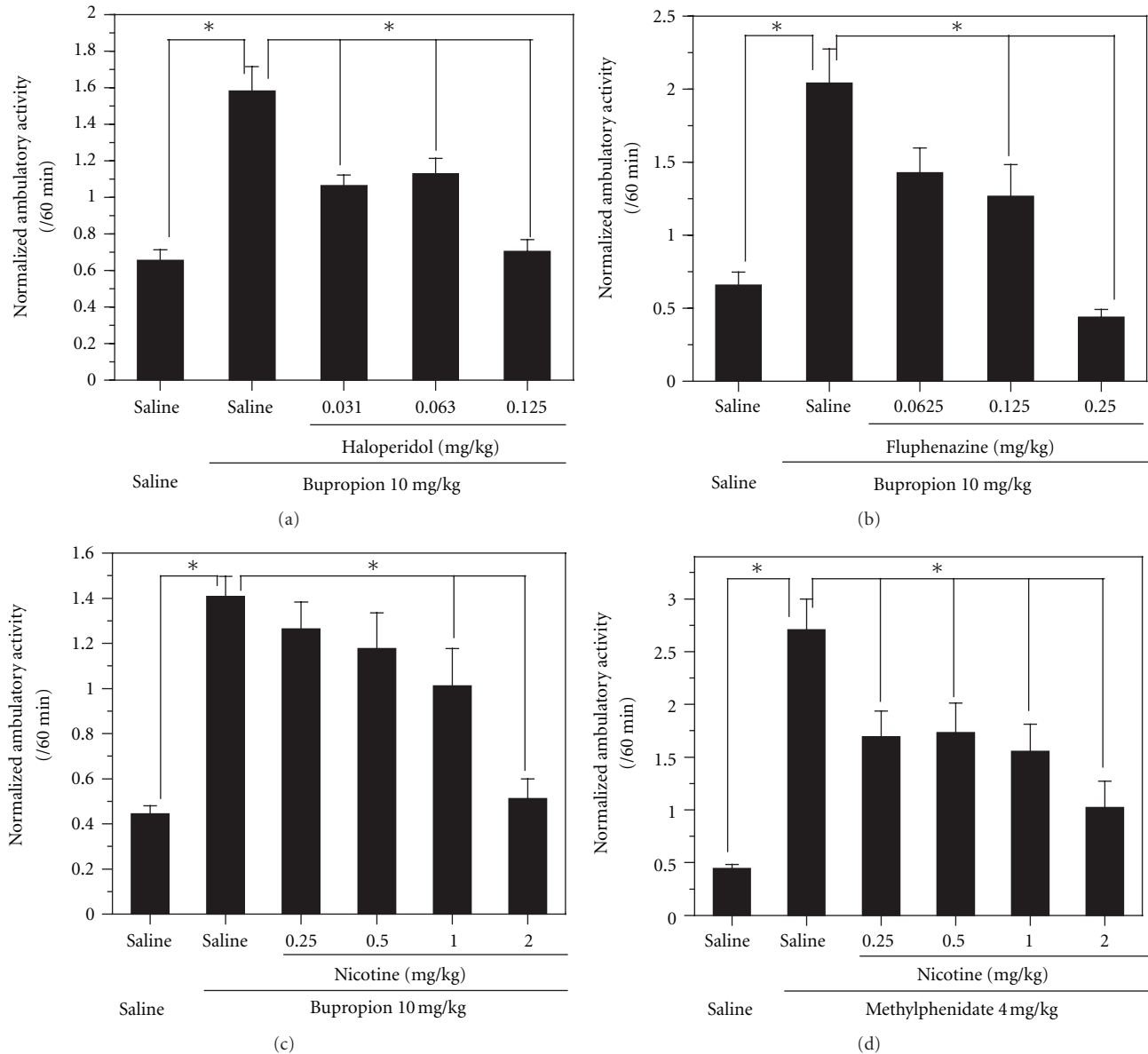


FIGURE 5: Effects of combined administrations of 10 mg/kg of BUP with 0.031–0.125 mg/kg of HAL (a), 0.0625–0.25 mg/kg of FLU (b), or 0.25–2 mg/kg of NIC (c) or combined administration of 4 mg/kg of MP with 0.25–2 mg/kg of NIC (d) on ambulatory activity in ICR mice. Filled columns represent mean values of ambulatory activity for 60 min after the administrations, and vertical lines indicate SEM. (a)  $N = 20-40$ , (b)  $N = 30-50$ , (c)  $N = 20-80$ , and (d)  $N = 20-40$ . \* $P < 0.05$  compared with BUP + saline or MP + saline.

behaviors (i.e., stereotypy) that are able to cause decrease of the ambulatory activity measurement of mice. However, NIC at 0.25–2 mg/kg did not produce such effect in ICR mice but animals exhibited less activity or sedation in the bucket-like activity cage. Because previous studies have also shown that 0.1–3 mg/kg of NIC produces hypoactivity on locomotion in ICR mice [60, 103, 104], it is possible to conclude that NIC acutely reduces locomotion in ICR mice. This locomotor effect of NIC in ICR mice is distinct from the effects of psychostimulants such as BUP and MP.

The idea that NIC exhibits distinct properties on locomotor effects from those of psychostimulants in ICR mice is further supported by results in the present study that examined effects of repeated administration of NIC, BUP, and MP. It is

well established that repeated administration of psychostimulants to the same animals produces augmented responses to these agents, a phenomena referred to as behavioral sensitization. BUP and MP also produce the same properties as psychostimulants on locomotor effects in rodents [105–109], and the properties of BUP and MP were confirmed in ICR mice in the present study. On the other hand, ICR mice developed tolerance against the inhibitory effect of NIC on the ambulatory activity when NIC was repeatedly administered. Thus, NIC produces unusual properties as a psychostimulant on locomotion in ICR mouse.

NIC exhibited effects similar to depressants such as HAL and FLU rather than psychostimulants such as BUP and MP on locomotion of ICR mice in this study; that is,

NIC reduced the ambulatory activity of ICR mice and the ambulation-stimulating effects of BUP and MP. These results suggest that NIC may lead to similar effects as HAL and FLU. It has been reported that NIC is able to ameliorate symptoms such as deficits of cognition and/or attention in animal models for psychosis as well as the effects of antipsychotics [110–117], indicating that NIC exhibits similar pharmacological properties to antipsychotics in animals. Thus, the idea in which NIC produces similar effects to antipsychotics in rodents has already been known; however, it has not been elucidated whether this notion is true for effects of NIC on rodent locomotion. The present study revealed that NIC exhibits similar effects as antipsychotics such as HAL and FLU on locomotion in ICR mice. Both BUP and MP are able to induce psychosis-like illnesses in humans [118–129], and the psychosis-like illnesses could be ameliorated by antipsychotics such as HAL and FLU. In light of these observations and the results of the present study, the self-medication hypothesis for heavy smoking among patients with schizophrenia [22–28] seems reasonable. NIC may reduce psychomotor excitation that accompanies with schizophrenia, and such efficacy of nicotine may be involved in heavy smoking in schizophrenia patients [29–35].

Neuronal acetylcholine receptors (nAChRs) could be involved in the inhibitory effect of NIC on ambulatory activity in ICR mice as the nAChRs antagonist, MECA, ameliorated the effect of NIC. nAChRs are known to be involved in the inhibitory effect of NIC on locomotion in C57Bl/6 mice [63, 130]. ICR mice developed tolerance against the inhibitory effect of NIC on ambulatory activity when NIC was repeatedly administered. C57Bl/6 mice also develop tolerance against the inhibitory effect on locomotion when NIC was chronically or repeatedly administered, and the development of tolerance is accompanied by changes in nAChRs in the brain [63, 130]. The involvement of nAChRs in the inhibitory effect of NIC and in the development of tolerance against the NIC effect on locomotion in C57Bl/6 mice suggests that nAChRs may play similar roles in locomotor effects of NIC in ICR mice.

The neurotransmitter dopamine (DA) might also be involved in the effects of NIC on ambulatory activity in ICR mice. Because both BUP and MP enhance DA neurotransmission through inhibition of its reuptake [96, 131–136], changes of DA neurotransmission could be involved in the ambulation-stimulating effects of these agents. The involvement of DA in the ambulation-stimulating effect of BUP in ICR mice is further supported by the present results in which both HAL and FLU, which possess DA receptor antagonizing abilities, reduced the ambulation-stimulating effect of BUP in ICR mice. Because effects of NIC observed in the present study were similar to those of HAL and FLU, it is probable that NIC influences DA neurotransmission to reduce ambulatory activity and the ambulation-stimulating effects of BUP and MP in ICR mice. Because nAChRs are directly and/or indirectly able to affect DA neurotransmission [137–140], interaction between nAChRs and the DA system might account for the effects of NIC on ambulatory activity in ICR mice.

## Acknowledgment

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