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Evidence for dopamine involvement in ambulation promoted by pulegone in mice

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ABSTRACT

I investigated whether dopamine (DA) is involved in the ambulation promoted by pulegone (PUL), a constituent of peppermint oil, in ICR mouse. Co-administration of PUL and bupropion (BUP) had an additive effect on their ambulation-promoting activities. When administered with PUL, the DA antagonists chlorpromazine, fluphenazine, haloperidol, SCH12679, and spiperone all attenuated the effect of PUL on ambulation. In addition, pretreatment with the DA depletor reserpine produced no subsequent sensitivity to the effect of PUL. Taken together, DA may be involved in the ability of PUL to promote ambulation in ICR mice but PUL may not be a direct DA agonist. The chemical structure of PUL is similar to menthol and menthone, and thus they may all be acting through a common mechanism.

1. Introduction

Interest in aromatherapy, which originated in ancient Egypt, has been increasing world-wide, and it is being revalued as an alternative medicine. Aromatherapy includes various treatment methods such as body and/or foot bathing, massage, and finger-pressure therapy; however, the most remarkable feature is the use of various kinds of plant-derived essential oils (EOs), hence the term aromatherapy. It has traditionally been believed that aromatherapy is able to treat various mental disorders (Tisserand, 1993) and that EOs are essential for producing such therapeutic effects. However, the absence of a scientific basis for their effectiveness has been noted (Balchin, 1997; Buckle, 1999). One possible explanation for the apparent efficacy of EOs on mental disorders is that EOs may possess psychoactive effects. Accumulating evidence (Perry and Perry, 2006), including that from our laboratory (Umezu, 1999, 2000, 2009; Umezu et al., 2001, 2002, 2006), is indicating that some EOs indeed produce pharmacological effects on animal behaviors similar to those of psychoactive drugs.

Peppermint oil has been believed to be useful in treating mental fatigue (Tisserand, 1993), which is not unreasonable as the oil promotes ambulation in ICR mice in a manner similar to psychostimulants (Umezu et al., 2001). This effect of peppermint oil is attributable to its constituent elements such as menthol (ME), menthone (MTN), isomenthone, 1,8-cineol, pulegone, menthyl acetate and caryophellene, as these constituents also promote mouse ambulation (Umezu et al., 2001). Peppermint oil and its constituents may have psychostimulant-like actions; however, whether their ambulation-promoting effects are a result of these pharmacological action(s) on CNS function is unclear, to say nothing of the mechanism(s) underlying the effects.

Dopamine (DA), a neurotransmitter, is thought to play an important role in controlling mouse ambulation. This notion is supported by the following findings: (1) direct and indirect DA agonists promote mouse ambulation (Kuribara and Tadokoro, 1984; Hirate and Kuribara, 1991; Asami et al., 1986; Kuribara and Uchihashi, 1993a); (2) such effects of DA agonists can be attenuated by combined administration with various DA antagonists (Kuribara and Uchihashi, 1993b, 1994; Kuribara, 1994a,b, 1995a, 1996); and (3) DA antagonists can also diminish the ambulation-promoting effects of non-DA agonists such as MK-801 and morphine (Kuribara et al., 1992; Kuribara, 1995b). Therefore, DA might also be involved in the mouse ambulation promoted by peppermint oil and its constituents.

Pharmacological methods that employ various agonists and antagonists that specifically act against some neurotransmitter systems are very useful for examining neurochemical mechanism(s) that might underlie behavioral effect(s) of the chemical in question in the absence of other successful methods. We previously used this technique to examine whether DA is involved in the ambulation-promoting effect of ME and MTN, major constituents of peppermint oil, in ICR mice (Umezu and Morita, 2003; Umezu, 2009). In those studies, we used a DA indirect agonist, bupropion (BUP), and various DA receptor antagonists. In addition, DA depletors such as reserpine and alpha-methyl-*p*-tyrosine were also used to determine whether peppermint constituents act directly on DA receptors. These examinations revealed that ME and MTN possess similar pharmacological properties as the DA indirect agonist BUP: (1) BUP, ME and MTN promote ambulation in ICR mice; (2) BUP and ME or MTN produces synergistic interactions on their ambulation-promoting effects when

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BUP and ME or MTN are simultaneously administered; (3) various DA antagonists reduce the abilities of BUP, ME and MTN to promote ambulation; and (4) DA depletors diminish the abilities of BUP, ME and MTN to promote ambulation (Umezu and Morita, 2003; Umezu, 2009). Thus, DA may be involved in the abilities of ME and MTN to promote ambulation in ICR mice but they may not be DA receptors direct agonists as well as BUP, a DA indirect agonist. Since ME and MTN are the major constituents of peppermint oil, DA may also be involved in the ambulation-promoting effect of the oil in ICR mice. However, the roles of other constituent elements in the ambulation-promoting effect of peppermint oil remain unclear. One important issue is whether DA is commonly involved in the ambulation-promoting effects of unexamined constituents of peppermint oil such as pulegone (PUL).

PUL is another major constituent of peppermint oil, constituting 3.2% of the peppermint oil used in our previous study (Umezu et al., 2001). PUL also promotes mouse ambulation. PUL has been known to be a skin penetration enhancer (Pillai and Panchagnula, 2003); antibacterial (Bekhechi et al., 2007; Sutour et al., 2008; Salehi et al., 2005); antifungal (Goncalves et al., 2007); insecticidal (Coats et al., 1991); antinociceptive (de Sausa et al., 2007); and to have antihistamine activity on guinea-pigs (Ortiz de Urbina et al., 1990). However, these previous findings do not provide any insight into the mechanism underlying its ambulation-promoting effect. The data on ME and MTN (Umezu and Morita, 2003; Umezu, 2009) suggest that DA is also involved in the ability of PUL to promote mouse ambulation. Thus, the current study examines this notion using the same pharmacological methods as those used for ME and MTN.

2. Materials and methods

The present study applied the same pharmacological protocol as those used for ME and MTN (Umezu and Morita, 2003; Umezu, 2009).

2.1. Animals

Male ICR mice (Clea Japan, Tokyo, Japan; 7–10 weeks old and body weight 35–42 g) were used. Commercial solid food (Clea Japan) and tap water were available *ad libitum*. The animals were kept under a 12 light:12 dark schedule (light period: 07:00–19:00) and at a constant room temperature of 25 ± 1 °C.

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

2.2. Drugs

The present study used PUL (5-Methyl-2-(1-methylethylidene) cyclohexanone), the DA indirect agonist BUP, the DA antagonists chlorpromazine (CPZ), fluphenazine (FLU), haloperidol (HAL), SCH12679 (SCH), and spiperone (SPI) and the DA depletor reserpine. These chemicals were purchased from Sigma-Aldrich (Tokyo). Olive oil, Tween 80 and NaCl were purchased from Nacalai Tesque (Kyoto), and acetic acid was from Wako Pure Chemicals (Osaka). These chemicals were used in preparing injection vehicles for DA-related agents.

2.3. Measurement of ambulatory activity in ICR mice

The present study measured the ambulatory activity of ICR mice using a tilt-type ambulometer (SAM-10; O'Hara and Co., Tokyo, Japan) to assess how DA relating agents modulate the ambulation-promoting effect of PUL. Details of the apparatus have already been reported (Hirabayashi et al., 1978; Umezu et al., 1998, 2001; Umezu and Morita, 2003; Umezu, 2009).

2.4. Experimental protocol

The ambulatory activity of individual ICR mouse was continuously measured in the following experiments, and the activity during the 60 min after the final administration of the agents was also recorded. Prior to each experiment, mice underwent a 30-min adaptation period in the activity cage. Olive oil and PUL were administered by intraperitoneal injection, and DA-related agents and their vehicles were administered subcutaneously.

2.4.1. Effect of intraperitoneal administration of PUL on ambulation

After the 30-min adaptation period, olive oil or 100, 200, 400 or 800 mg/kg of PUL was administered to the mice followed by a 60-min measurement of ambulatory activity.

2.4.2. Interaction between PUL and BUP on ambulatory activity

After the 30-min adaptation period, saline or 1.25, 2.5 or 5 mg/kg of BUP was administered, followed 10 min later by administration of olive oil or 100 or 200 mg/kg of MTN.

2.4.3. Effects of DA antagonists on the ambulation-promoting effect of PUL

After the 30-min adaptation period, 0.25–1 mg/kg of CPZ, 0.063–0.25 mg/kg of FLU, 0.032–0.125 mg/kg of HAL, 2.5–10 mg/kg of SCH, or 0.032–0.125 mg/kg of SPI was administered, followed 10 min later by administration of 200 mg/kg of PUL. As control experiments, the effects of the combined administration of the same doses of CPZ, FLU, HAL, SCH or SPI with olive oil were also examined under the same protocol.

2.4.4. Effects of pretreatment with RES on the ambulation-promoting effect of PUL

Saline or 8 or 16 mg/kg of RES was administered and 1 day later, after the 30-min adaptation period 400 mg/kg of PUL was administered.

2.5. Statistical analysis

The time course of ambulatory activity after administration of PUL was initially examined using repeated-measures analysis of variance (ANOVA). Differences in total ambulatory activity over 1 h were then analyzed using ANOVA, followed by Fisher's PLSD test. When PUL was combined with BUP, data were analyzed using two-way ANOVA. The effects of the DA antagonists and pre-administration of RES were analyzed using ANOVA. $P<0.05$ was established as the level of significance.

3. Results

3.1. Effect of intraperitoneal administration of PUL on ambulation

Intraperitoneal administration of PUL significantly promoted ambulation in the ICR mice. Fig. 1a shows the time course of the ambulatory activity after administration of olive oil or various doses of PUL. The effects of dose, time course and their interaction were statistically significant (repeated-measures ANOVA; dose ($F(4, 252) = 2.727$, $P<0.05$); time course ($F(5, 1260) = 90.452$, $P<0.05$; their interaction ($F(20, 1260) = 6.754$, $P<0.05$). Fig. 1b shows the total ambulatory activity during the 60 min after PUL administration. PUL increased total ambulatory activity in a dose-dependent but bell-shaped manner ($F(4, 253) = 2.728$, $P<0.05$; Fisher's PLSD test: differences from control, 100 mg/kg = −55.56, $P>0.05$; 200 mg/kg = −125.85, $P=0.043$; 400 mg/kg = −181.9, $P<0.0001$; 800 mg/kg = −114.15, $P>0.05$).

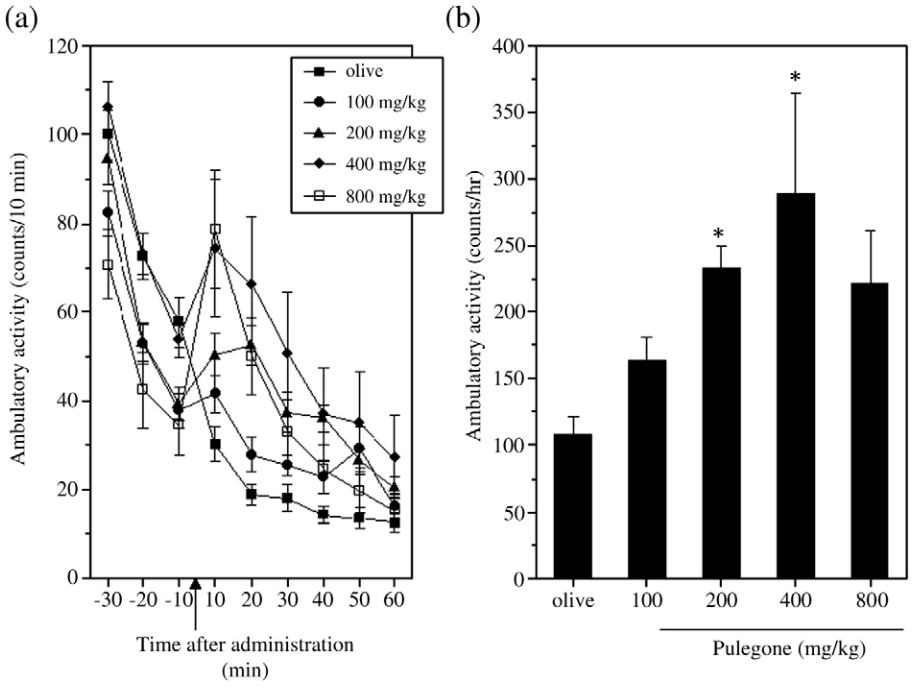

Fig. 1. Ambulatory activity in ICR mice after intraperitoneal administration of PUL. a: Changes in ambulation after intraperitoneal administration of PUL. Symbols represent mean values of ambulation for 10-min periods, and vertical lines indicate standard error of the mean (SEM). $N = 20–80$ animals per dose group. Arrow indicates time of PUL administration. b: Total ambulation over 60 min after administration of olive oil or various doses of PUL. Filled columns indicate mean values of total ambulation for 60 min, and vertical lines indicate SEM. Data were analyzed by ANOVA, followed by Fisher's PLSD test. $^*P<0.05$ compared with control values obtained after olive oil administration.

3.2. Interaction between PUL and BUP on ambulatory activity

Fig. 2 shows the mean total ambulatory activity caused by combined administration of various doses of PUL with various doses of BUP. PUL and BUP produced significant ambulation-promoting effects but their statistical interaction was not significant (Two-way ANOVA; effect of PUL $F(2, 225) = 8.443$, $P<0.05$; effect of BUP, $F(3, 225) = 3.981$, $P<0.05$; their interaction, $F(6. 225) = 0.375$, $P>0.05$), indicating that the ambulation-promoting effect of PUL interacts with those of BUP in an additive manner.

3.3. Effects of DA antagonists on the ambulation-promoting effect of PUL

Fig. 3a–e shows the effects of various DA antagonists on ambulation promoted by 200 mg/kg of PUL. The figures also show the results of co-administration of the DA antagonists with olive oil. All DA antagonists attenuated the ambulation-promoting effect of 200 mg/kg of PUL, and their effects on baseline ambulatory activity did not account for their effects on the effect of PUL. Thus, all examined DA antagonists attenuated the ability of PUL to promote ambulation.

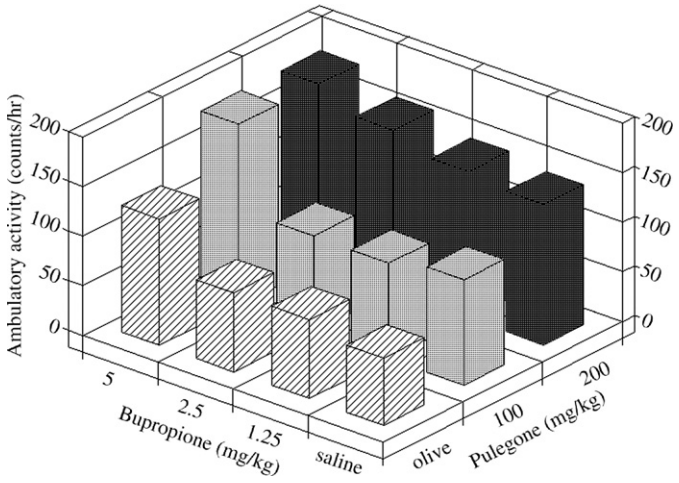

Fig. 2. Effects of various doses of BUP plus PUL on ICR mouse ambulation. Columns indicate mean values of total ambulatory activity for 60 min after administration of BUP combined with PUL. $N = 19–20$ mice per group.

CPZ, HAL and SCH significantly suppressed the ambulation-promoting effect of 200 mg/kg of PUL in ICR mice in a dose-dependent manner (CPZ, Fig. 3a closed columns; $F(3, 76) = 4.301$, $P<0.05$); differences from control, 0.25 mg/kg = 69.3; 0.5 mg/kg = 152.65 ($P = 0.0043$); 1 mg/kg = 161 ($P = 0.0027$); HAL, Fig. 3c closed columns; $F(3, 76) = 12.251$, $P<0.05$; differences from control, 0.032 mg/kg = 105.3 ($P = 0.0012$); 0.063 mg/kg = 122.45 ($P = 0.0002$); 0.125 mg/kg = 185.95 ($P<0.0001$); and SCH, Fig. 3d closed columns; $F(3, 76) = 18.604$, $P<0.05$; differences from control, 2.5 mg/kg = 148.3 ($P<0.0001$); 5 mg/kg = 140.75 ($P<0.0001$); 10 mg/kg = 214.9 ($P<0.0001$)). However, these DA antagonists did not suppress the ambulatory activity when co-administered with olive oil (CPZ, Fig. 3a open columns; ($F(3, 68) = 0.394$, $P>0.05$); differences from control, 0.25 mg/kg = 1.444; 0.5 mg/kg = −9.278; 1 mg/kg = −3.5; HAL, Fig. 3c open columns; ($F(3, 68) = 1.591$, $P>0.05$; differences from control, 0.032 mg/kg = 10.333; 0.063 mg/kg = 6.944; 0.125 mg/kg = 11.833; SCH, Fig. 3d open columns; $F(3, 37) = 1.741$, $P>0.05$; differences from control, 2.5 mg/kg = 16.021; 5 mg/kg = 13.688; 10 mg/kg = 15.132)). FLU and SPI also suppressed the ambulation-promoting effects of 200 mg/kg of PUL (FLU, Fig. 3b closed columns; $F(3, 95) = 3.983$, $P<0.05$; differences from control, 0.063 mg/kg = 65.95; 0.125 mg/kg = 58.603; 0.25 mg/kg = 151.25 ($P = 0.0009$); and SPI, Fig. 3e closed columns; $F(3, 76) = 17.173$, $P<0.05$; differences from control, 0.032 mg/kg = 158.5 ($P<0.0001$); 0.063 mg/kg = 217.65 ($P<0.0001$); 0.125 mg/kg = 240.7 ($P<0.0001$)). These DA antagonists significantly decreased the ambulatory activity when co-administered with olive oil, but only to a small extent (FLU, Fig. 3b open columns; ($F(3, 64) = 4.271$, $P<0.05$; differences from control, 0.063 mg/kg = 16.243 ($P = 0.0135$); 0.125 mg/kg = 11.812; 0.25 mg/kg = 22.188 ($P = 0.0009$); and SPI,

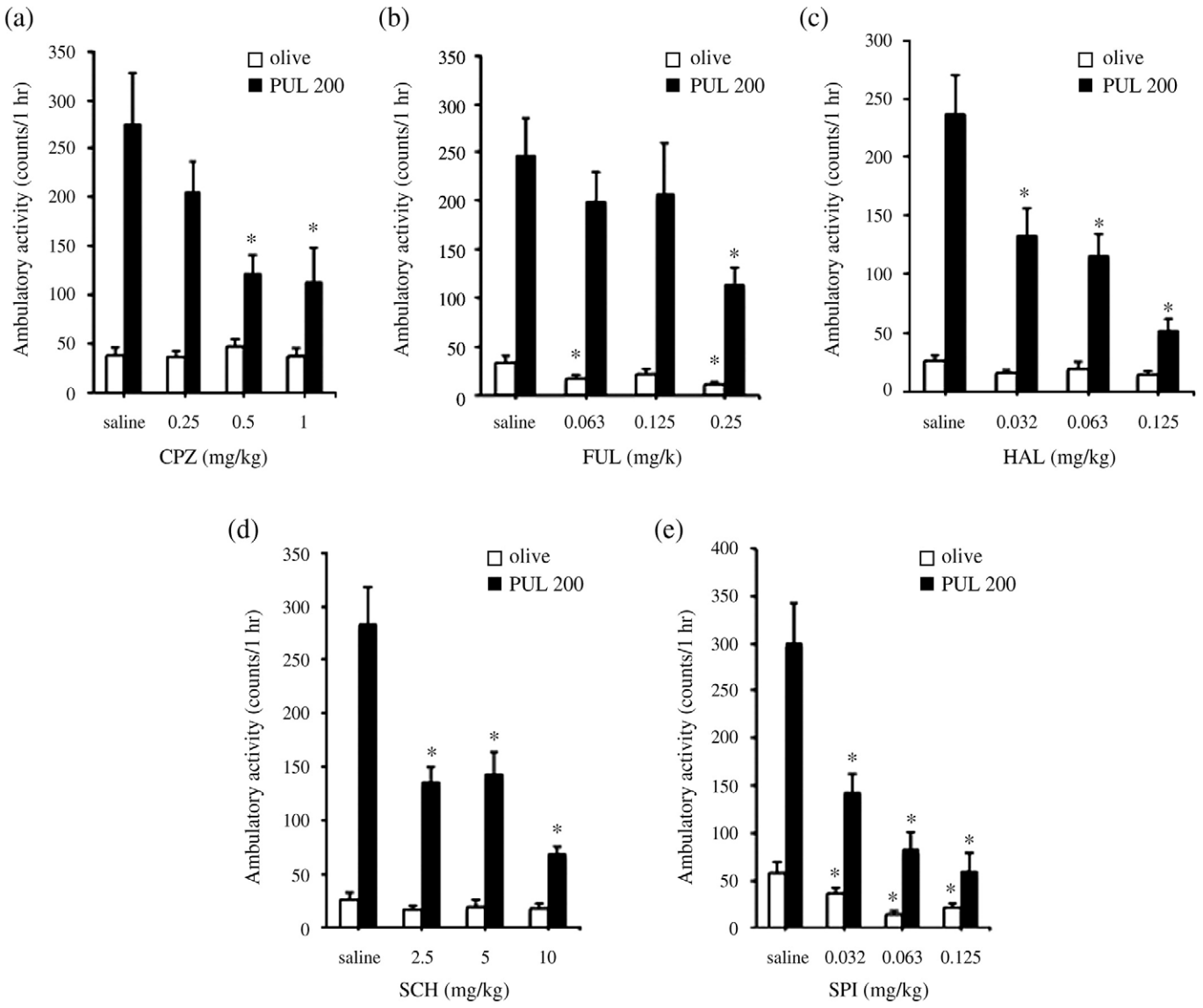

Fig. 3. Open columns: ambulatory activity in ICR mice after administration of 200 mg/kg of PUL with (a) 0.25–1 mg/kg of chlorpromazine (CPZ) ($N=20$), (b) 0.063–0.25 mg/kg of fluphenazine (FLU) ($N=19$–40), (c) 0.032–0.125 mg/kg of haloperidol (HAL) ($N=20$), (d) 2.5–10 mg/kg of SCH12679 (SCH) ($N=20$) or (e) 0.032–0.125 mg/kg of spiperone (SPI) ($N=20$). Closed columns: ambulatory activity in ICR mice after administration of olive oil with (a) 0.25–1 mg/kg of chlorpromazine (CPZ) ($N=18$), (b) 0.063–0.25 mg/kg of fluphenazine (FLU) ($N=16$–18), (c) 0.032–0.125 mg/kg of haloperidol (HAL) ($N=18$), (d) 2.5–10 mg/kg of SCH12679 (SCH) ($N=7$–16) or (e) 0.032–0.125 mg/kg of spiperone (SPI) ($N=18$).

Fig. 3e open columns; $F(3, 68)=7.402$, $P<0.05$; differences from control, 0.032 mg/kg = 21.222 ($P=0.037$); 0.063 mg/kg = 43.5 ($P<0.0001$); 0.125 mg/kg = 36.111 ($P=0.0006$)).

3.4. Effects of pretreatment with RES on the ambulation-promoting effect of PUL

Pretreatment with the DA depletor RES significantly attenuated the ambulation-promoting effect of PUL (Fig. 4) (($F(2, 57)=6.559$, $P<0.05$); differences from control, 8 mg/kg = 103.7 ($P=0.0017$); 16 mg/kg = 93.3 ($P=0.0045$)).

4. Discussion

As previously reported (Umezu et al., 2001), intraperitoneal injection of PUL promotes ambulation in ICR mice. The results obtained in the current study indicate that DA may be involved in the ability of PUL to promote ambulation in ICR mice, since (1) PUL interacted with a DA indirect agonist BUP to increase the ambulation-promoting effect in an additive manner, and (2) various DA antagonists suppressed the ability of PUL to promote ambulation. In addition, PUL may not be a direct DA receptor agonist given that pretreatment with the DA depletor RES eliminated the sensitivity to the effect of PUL. These pharmacological properties of PUL are the same as those of the DA indirect agonist BUP (Umezu and Morita, 2003), which further supports DA involvement in the ambulation promoted by PUL. Thus, PUL may produce psychoactive action similar to the already known psychostimulants, at least in part through acting on the DA system in the CNS.

The pharmacokinetics of peripherally administered PUL have not been well examined. Since a previous study demonstrated that a much lower dose of PUL promotes ambulation when injected intravenously, peripherally administered PUL is likely to be absorbed into the bloodstream and then cross the blood–brain barrier, where it acts on neurons in the brain in the same manner as psychoactive drugs. The pharmacokinetics of PUL warrant further examination.

It has been well established that DA is involved in spontaneous motor activity promoted by various psychoactive drugs in rodents.

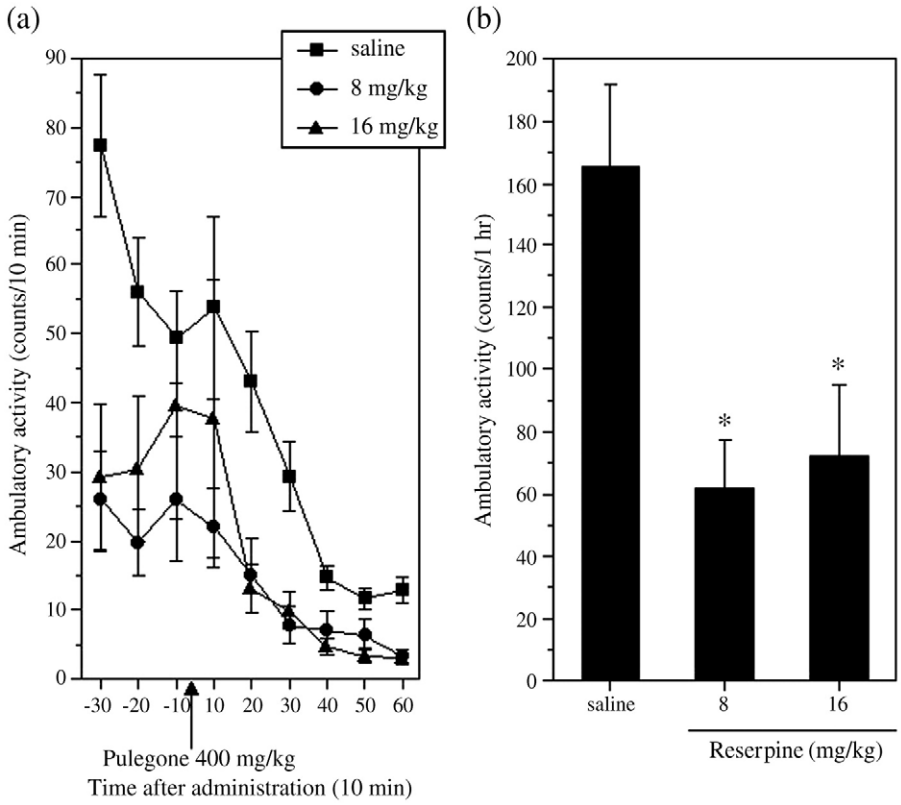

Fig. 4. Effect of prior exposure to various doses of reserpine (RES) on the effect of 400 mg/kg of PUL in ICR mice ($N = 20$). RES was administered 1 day before PUL. See details in legend to Fig. 1.

This also holds true for the ambulatory activity of mice, a type of spontaneous motor activity in mice, as numerous studies (Kuribara and Uchihashi, 1993b, 1994; Kuribara, 1994a,b, 1995a,d, 1996) have demonstrated the involvement of DA in the ambulation-promoting effects of various psychoactive drugs (Kuribara and Tadokoro, 1983, 1984; Asami et al., 1986; Iijima et al., 1986; Hirate and Kuribara, 1991; Kuribara and Uchihashi, 1993a; Kuribara et al., 1990, 1991; Kuribara, 1994c,d, 1995c). The present study was conducted based upon these previous findings since PUL also promotes ambulation in ICR mice.

To test the possibility of DA involvement in the ambulation promoted by PUL in ICR mice, the current study used various DA-related drugs as well as data from our previous studies (Umezu and Morita, 2003; Umezu, 2009). BUP is an indirect DA agonist, as it inhibits DA uptake in nerve terminals (Gazzara and Andersen, 1997; Munzar and Goldberg, 2000). Studies have shown that BUP promotes ambulation in mice (Umezu and Morita, 2003), similar to other indirect DA agonists (Kuribara and Uchihashi, 1993a,b, 1994; Kuribara, 1994a,b,c,d, 1995a,d, 1996), and that various DA antagonists attenuate the ambulation-promoting effect of BUP (Umezu and Morita, 2003), and thus BUP may be acting as a DA indirect agonist. We demonstrated here that both BUP and PUL promote ambulation and interact in an additive manner to further promote mouse ambulation, suggesting that BUP and PUL share a common mechanism for promoting mouse ambulation. Thus, DA may be involved in the ability of PUL to promote ambulation in ICR mice.

CPZ, FLU, HAL, SCH and SPI are DA receptor antagonists. They inhibit the CNS actions of endogenous DA and exogenous DA agonists through inhibition of the binding of these compounds to the DA receptors in the CNS. These DA antagonists suppressed the mouse ambulation promoted by PUL in the present study. Since the current study used these DA antagonists at doses that have been shown to reduce the ability of BUP to promote ambulation (Umezu and Morita, 2003), they should be sufficient to suppress the ambulation-promoting effect of PUL if DA is involved in the effect. On the other hand, these DA antagonists might suppress the effect of PUL by decreasing the basal ambulatory activity of mice through inhibiting the action of endogenous DA. However, this notion is not the case for CPZ, SCH and HAL, since the tested doses of CPZ, SCH and HAL did not reduce ambulation when combined with olive oil. This notion may partly be true in the cases of FLU and SPI, since they tended to decrease ambulatory activity when combined with olive oil. However, FLU and SPI decreased basal ambulatory activity only to a minor extent; thus, changes in behavioral baseline activity by FLU and SPI cannot sufficiently account for suppression of the ambulation promoted by PUL. Thus, FLU and SPI also reduce the ability of PUL to promote mouse ambulation. The attained results provide further evidence for the involvement of DA in the ambulatory effects of PUL.

However, we had not determined whether PUL acts as a DA direct agonist. We used the DA depletory RES to solve this problem since RES depletes DA stores, thereby reducing DA efflux (Silva et al., 2002; Matsuda et al., 2000) and resulting in super sensitivity to DA direct agonists (Rubinstein et al., 1988) and decreased sensitivity to DA indirect agonists (Wacan et al., 2006; Umezu and Morita, 2003). As RES reduced the ambulatory effect of PUL, PUL may not act as a direct agonist on DA receptors.

PUL is distinguishable from already known indirect DA agonists such as methamphetamine or cocaine, which increase extracellular DA level through inhibition of DA uptake and/or by facilitating DA release to promote ambulation, since those already known indirect DA agonists cause stereotyped behavior at high doses but large doses of PUL produce ataxia. Thus, PUL promotes ambulation through changing extracellular DA levels likely by a mechanism different from those of the already known DA indirect agonists. Alternatively, PUL may act on another neurotransmitter system in addition to the DA system at the same time to produce ataxia. It is also probable that the DA system may be downstream of PUL's target(s): for example,

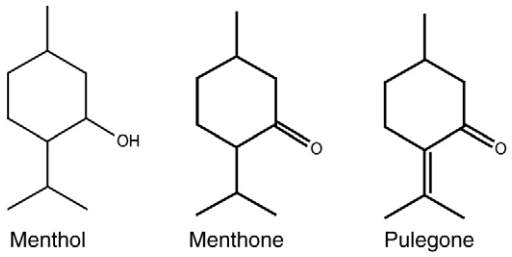

Fig. 5. Chemical structures of menthol, menthone, and pulegone.

MK-801 produces ambulation-promoting effects and ataxia in mice (Iijima et al., 1986; Kuribara et al., 1992) by antagonizing inhibitory NMDA receptors upstream of the DA system. However, it is not known whether PUL affects the glutaminergic system. Although the precise mechanism for the ambulation-promoting effect of PUL remains unclear at present, the current results suggest that DA is involved in the ambulation-promoting effect of PUL in ICR mice.

The results observed in this study are identical with those of ME (Umezu and Morita, 2003) and MTN (Umezu, 2009), whose chemical structures are similar to PUL (Fig. 5). The mechanism underlying the ambulatory effects of these agents might be identical, and those structural properties might provide insight for determining their target(s) in the CNS. Since those compounds have similar chemical structures and action properties, they could interact via the same mechanism in an additive manner to change extracellular DA levels, which would explain the ambulatory effects of peppermint oil. The ambulation-promoting effect of peppermint oil in mice could be a product of pharmacological actions of its constituents on CNS that are similar to those of psychostimulants, which would account for some of the traditional therapeutic efficacies of peppermint oil (Tisserand, 1993).

Acknowledgment

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