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Intrastriatal injection of opioid receptor agonists inhibits apomorphine-induced behavior in 6-hydroxydopamine-treated mice

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Abstract

The effects of intrastriatal (i.st.) injections of μ-, δ- and κ-selective opioid receptor agonists on the augmentation of apomorphine-induced behaviors were determined in 6-hydroxydopamine-treated mice by using multidimensional behavioral analyses. 6-Hydroxydopamine (16 μg/μl, i.st.) was unilaterally injected into the striatum 30 min after pretreatment with desipramine (25 mg/kg, s.c). Mice were tested 14 days after injection of 6-hydroxydopamine. Apomorphine (0.5 mg/kg, s.c.) produced a marked increase in linear locomotion, contralateral circling and/or rearing behavior in 6-hydroxydopamine- but not vehicle-treated mice. Although the μ-selective opioid receptor agonist [D-Ala^2,*N*-Me-Phe^4,Gly^5-ol]enkephalin (DAMGO) (0.1 and 0.3 ng, i.st.) or the κ-selective opioid agonist dynorphin A-(1–13) (0.1 and 0.3 μg, i.st.) did not produce any significant effects on behavior, these peptides had an inhibitory effect on the apomorphine (0.5 mg/kg, s.c.)-induced increase in behavioral responses such as linear locomotion, contralateral circling and/or rearing behavior in 6-hydroxydopamine-treated mice. The inhibitory effects of DAMGO (0.3 ng, i.st.) and dynorphin A-(1–13) (0.3 μg, i.st.) were fully reversed by selective opioid receptor antagonists such as β-funaltrexamine (5 μg, i.c.v.) and (−)-(1*R*,5*R*,9*R*)-5,9-diethyl-2-(3-furyl-methyl)-2′-hydroxy-6,7-benzomorphan (Mr2266) (10 mg/kg, s.c.), respectively. In contrast, the δ-selective opioid receptor agonist [D-Pen^2,L-Pen^5]enkephalin (DPLPE) (0.03, 0.1 or 0.3 μg, i.st.) had no marked effects on the apomorphine (0.5 mg/kg, s.c.)-induced behavior in 6-hydroxydopamine-treated mice. These results suggest that the stimulation of μ- and κ- but not δ-opioid receptors plays an inhibitory role in the behavioral augmentation induced by the activation of postsynaptic dopamine receptors in the striatum sensitized with 6-hydroxydopamine.

Keywords: DAMGO ([D-Ala^2,*N*-Me-Phe^4,Gly^5-ol]enkephalin); DPLPE ([D-Pen^2,L-Pen^5]enkephalin); Dynorphin A-(1–13); 6-Hydroxydopamine; Apomorphine; (Mouse)

1. Introduction

Increasing evidence suggests that opioid receptor agonists can modulate the activity of mesolimbic and nigrostriatal dopaminergic neurons (Di Chiara and Imperato, 1988; Spanagel et al., 1990). Specifically, it has been shown that μ- as well as δ-selective opioid receptor agonists stimulate dopamine release in both the nucleus accumbens and striatum, whereas κ-selective opioid receptor agonists inhibit dopamine release. In fact, there are some reports supporting the existence of tonically active opioidergic neurons, which regulate the basal activity of mesolimbic dopamine neurons (Giorgi et al., 1991; Spanagel et al., 1992).

We have previously analysed in detail the effects of selective opioid receptor agonists on dopamine-mediated behavioral responses. For example, intracerebroventricular injections of the μ-selective opioid receptor agonist [D-Ala^2,*N*-Me-Phe^4,Gly^5-ol]enkephalin (DAMGO) and the κ-selective opioid receptor agonist dynorphin A-(1–13) produce an antagonistic effect on the apomorphine-induced increase in rearing behavior (Ukai et al., 1989a, 1991, 1992), whereas the D_2-selective dopamine receptor agonist *N*-phenethyl-*N*-propyl-2-(3-hydroxyphenyl)ethylamine (RU 24213)-induced increase in linear locomotion, circling, rearing and grooming behavior is almost completely reversed by

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DAMGO and dynorphin A-(1–13) but not by [D-Pen^2,L-Pen^5]enkephalin (DPLPE) (Toyoshi et al., 1991; Ukai et al., 1992). Nevertheless, the site where DAMGO and dynorphin A-(1–13) modify the behavioral effects of dopamine receptor agonists is unclear, although opioid receptors have been localized in pre- and postsynaptic dopamine neurons in the striatum.

In the present study, the effects of intrastriatal injection of μ-, δ- and κ-selective opioid receptor agonists on the apomorphine-induced behavioral alteration in 6-hydroxydopamine-treated mice were examined by using multidimensional behavioral analyses (Kameyama and Ukai, 1981, 1983; Ukai et al., 1989b; Toyoshi et al., 1991, 1992) in order to clarify the site of action of opioid receptor agonists on the apomorphine-induced behavioral alteration. In addition, the effects of DAMGO and dynorphin A-(1–13) were characterized with opioid receptor antagonists such as β-funaltrexamine (Portoghese et al., 1980) and (−)-(1*R*,5*R*,9*R*,)-5,9-diethyl-2-(3-furyl-methyl)-2′-hydroxy-6,7-benzomorphan (Mr2266) (Roemer et al., 1980; Ukai et al., 1989a, 1992), respectively, while 6-hydroxydopamine combined with desipramine was injected into the striatum to destroy nigrostriatal dopamine neurons.

2. Materials and methods

2.1. Animals

Male ddY mice (Nihon SLC, Hamamatsu, Japan) weighing between 30 and 35 g were used in the experiments. The animals were randomly assigned to groups consisting of 10 mice per group. Before the experiments, mice were given free access to food and water, and individual mice were housed in a cage in a constantly illuminated room at a temperature of 23 ± 1°C and a relative humidity of 55 ± 2.5%. The mice were used only once and were unfamiliar with the test box. The experiments were conducted between 10:00 a.m. and 6:00 p.m. in a sound-attenuated room.

2.2. Intrastriatal injections

The unilateral injection was internal (1 mm) and caudal (1 mm) to the right orbitus (Worms et al., 1986, 1987). The injection was made with a 5-mm long needle (30 gauge; final length below the skin, 3.5 mm) attached to a 10-μl Hamilton microsyringe. The needle was inserted perpendicularly through the skull and into the right striatum of the brain under brief ether anesthesia. Drug solutions were injected in a volume of 1 μl per mouse over a period of 20 s. The site was checked by injecting a 1:10 dilution of India ink in isotonic saline (0.9% NaCl, pH 7.5). Histological examinations revealed particles of the ink in the right striatum.

2.3. Lesions with 6-hydroxydopamine

Mice were injected with 6-hydroxydopamine (16 μg/μl, free base) unilaterally into the right striatum 30 min after pretreatment with desipramine (25 mg/kg) (Pycock et al., 1977). Mice were tested 14 days after the injection of 6-hydroxydopamine, and those animals circling tightly away from the lesioned side following subcutaneous administration of apomorphine (0.5 mg/kg) were selected for the experiment.

2.4. Multidimensional analysis

Behavior was observed over a period of 15 min. The Animex II, equipped with a personal computer, was used for measuring behavior (Kameyama and Ukai, 1981, 1983; Ukai et al., 1989a). The sensor consisted of three pairs of electrodes and formed a capacitor bridge. Once a mouse was placed in the space (150 × 210 × 140 mm) between the electrodes connected to field detectors, the value of the capacitor then depended upon the location of mouse within that space. When converting the analog signal received by the detectors to a digital form, the d.c. voltage movement spectrum analyser classified movement into 9 degrees (1/1, 1/2, 1/4, 1/8, 1/16, 1/32, 1/64, 1/128 and 1/256). Behavioral responses (ambulation, circling, rearing and grooming) could be detected along the length of the cage (210 mm) and on the sides of the cage (140 mm × 2). Thus, the counters were placed to detect the following magnitudes of movements: 1/1 (×490 mm) = 490 mm, 1/2 (×490 mm) = 245 mm, 1/4 (×490 mm) = 122.5 mm, 1/8 (×490) = 61.3 mm, 1/16 (×490 mm) = 30.6 mm, 1/32 (×490 mm) = 15.3 mm, 1/64 (×490 mm) = 7.7 mm, 1/128 (×490 mm) = 3.8 mm, and 1/256 (×490 mm) = 1.9 mm. The movement of greatest magnitude was principally registered on the 1/1 counter and the movement of the smallest magnitude, such as tremor, on the 1/256 counter. Specific patterns of behavior, induced by a drug, were registered on the counters as follows, linear locomotion on 1/1, circling on 1/4, rearing on 1/16 and grooming on 1/64 (Kameyama and Ukai, 1983). In addition, the circling behavior mentioned above includes movement of the animal along all sides and corners of the testing cage. The sensitivity (%) of the device was adjusted according to the body weight (g) as follows, 30–31 g = 23% and 32–35 g = 22%. Each value in the figures is the ratio mean ± S.E. after ratios were calculated for each of the animals. The ratios for each of the animals equalled the actual values of drug-treated animals divided by the mean actual values of controls.

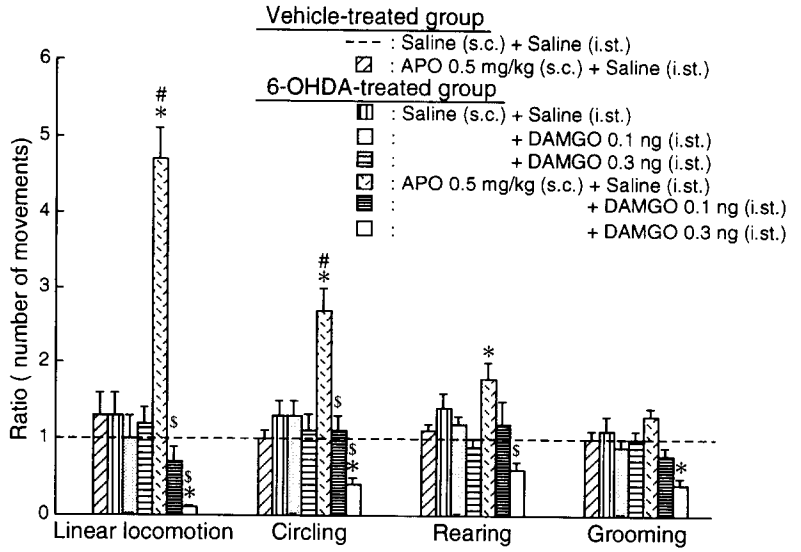

Fig. 1. Movements made by mice after the administration of apomorphine (APO) (0.5 mg/kg, s.c.), DAMGO (0.1 and 0.3 ng, i.st.) and their combinations. Values represent the mean ± S.E. for 10 mice. * Denotes significant difference from vehicle control, $P < 0.05$. # Denotes significant difference from vehicle + APO (0.5 mg/kg, s.c.), $P < 0.05$. $ Denotes significant difference from 6-hydroxydopamine (6-OHDA) + APO (0.5 mg/kg, s.c.), $P < 0.05$.

2.5. Drugs

Desipramine hydrochloride, 6-hydroxydopamine hydrobromide, apomorphine hydrochloride (Sigma, St. Louis, USA), DAMGO, DPLPE (Peninsula Laboratories, Belmont, USA), dynorphin A-(1–13) (Peptide Institute, Minoh, Japan), β-funaltrexamine hydrochloride (Research Biochemicals, Natick, USA) and (−)-(1*R*,5*R*,9*R*,)-5,9-diethyl-2-(3-furyl-methyl)-2′-hydroxy-6,7-benzomorphan (Mr2266) (Boehringer Ingelheim, Ingelheim am Rhein, Germany) were used throughout. Desipramine, DAMGO, DPLPE, dynorphin A-(1–13) and β-funaltrexamine were dissolved in isotonic saline (0.9% NaCl, pH 7.5). Mr2266 was dissolved in 1 ml

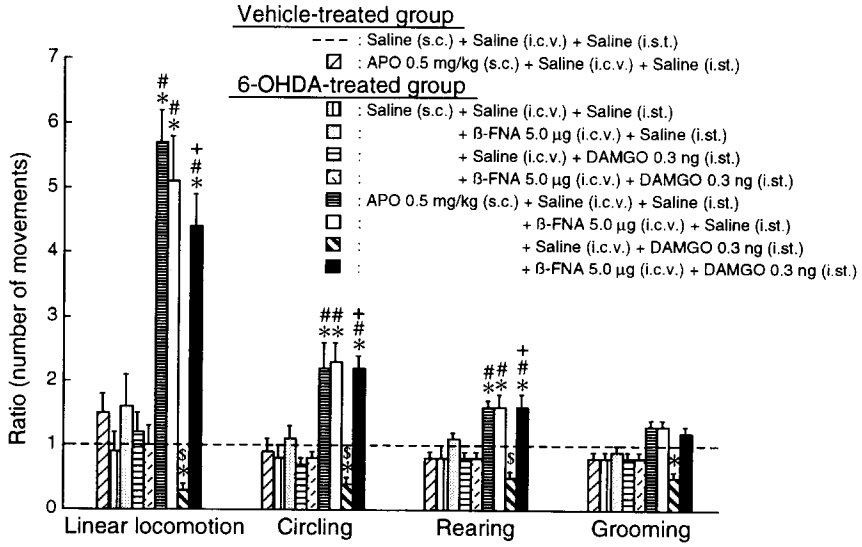

Fig. 2. Movements made by mice after the administration of apomorphine (APO) (0.5 mg/kg, s.c.), DAMGO (0.3 ng, i.st.), β-funaltrexamine (β-FNA) (5 µg, i.c.v.) and their combinations. Values represent the mean ± S.E. for 10 mice. * Denotes significant difference from vehicle control, $P < 0.05$. # Denotes significant difference from vehicle + APO (0.5 mg/kg, s.c.), $P < 0.05$. $ Denotes significant difference from 6-hydroxydopamine (6-OHDA) + APO (0.5 mg/kg, s.c.), $P < 0.05$. + Denotes significant difference from 6-hydroxydopamine (6-OHDA) + APO (0.5 mg/kg, s.c.) + DAMGO (0.3 ng, i.st.), $P < 0.05$.

5%w/v (±)-tartaric acid and the volume was made up with 0.9% saline. The vehicle for 6-hydroxydopamine and apomorphine was 0.9% saline containing 0.1% ascorbic acid. Apomorphine (s.c.), β-funaltrexamine (i.c.v.), Mr2266 (s.c.) and peptides (i.st.) were administered 25 min, 22–24 h, 15 min and 10 min, respectively, before the start of behavioral measurements.

2.6. Data analysis

Data for actual values were analysed statistically by means of a one-factor analysis of variance (ANOVA). Post-hoc analysis for between-group differences was carried out by the Newman-Keuls method for multiple comparisons (Zar, 1984). Effects were considered statistically significant if $P < 0.05$. Data in figures indicate ratios derived from actual values for the clearer presentation of results.

3. Results

3.1. Effects of DAMGO

ANOVA revealed a significant relation of behavioral responses in vehicle- and 6-hydroxydopamine-treated groups ($P < 0.01$): $F(7,72) = 31.88$ for linear locomotion, $F(7,72) = 10.78$ for circling, $F(7,72) = 4.07$ for rearing and $F(7,72) = 6.39$ for grooming (Fig. 1). A 0.5 mg/kg dose of apomorphine produced a marked increase in linear locomotion, contralateral circling and rearing in 6-hydroxydopamine- but not vehicle-treated mice (Fig. 1). DAMGO (0.1 or 0.3 ng) had no significant effects on these behaviors, but almost completely inhibited the marked increase in these behaviors induced by apomorphine (0.5 mg/kg) (Fig. 1).

3.2. Effects of β-funaltrexamine on the effects of DAMGO

ANOVA showed a significant relation of behavioral responses in vehicle- and 6-hydroxydopamine-treated groups ($P < 0.01$): $F(9,90) = 22.59$ for linear locomotion, $F(9,90) = 10.88$ for circling, $F(9,90) = 7.69$ for rearing and $F(9,90) = 5.16$ for grooming (Fig. 2). Although β-funaltrexamine (5 μg) alone did not affect the behavioral patterns, the inhibitory effects of DAMGO (0.3 ng) on the apomorphine (0.5 mg/kg)-induced behavioral responses were completely reversed by β-funaltrexamine (5 μg) (Fig. 2).

3.3. Effects of DPLPE

ANOVA revealed a significant relation of behavioral responses in vehicle- and 6-hydroxydopamine-treated groups ($P < 0.01$): $F(9,90) = 14.72$ for linear locomotion, $F(9,90) = 22.44$ for circling and $F(9,90) = 7.23$ for rearing (Fig. 3). DPLPE (0.03, 0.1 or 0.3 μg) had no significant effects on these behaviors, while a 0.5 mg/kg dose of apomorphine again produced a marked increase in linear locomotion, contralateral circling and rearing in 6-hydroxydopamine-treated mice (Fig. 3). DPLPE (0.03, 0.1 and 0.3 μg) failed to affect the behavioral changes induced by a 0.5 mg/kg dose of apomorphine (Fig. 3).

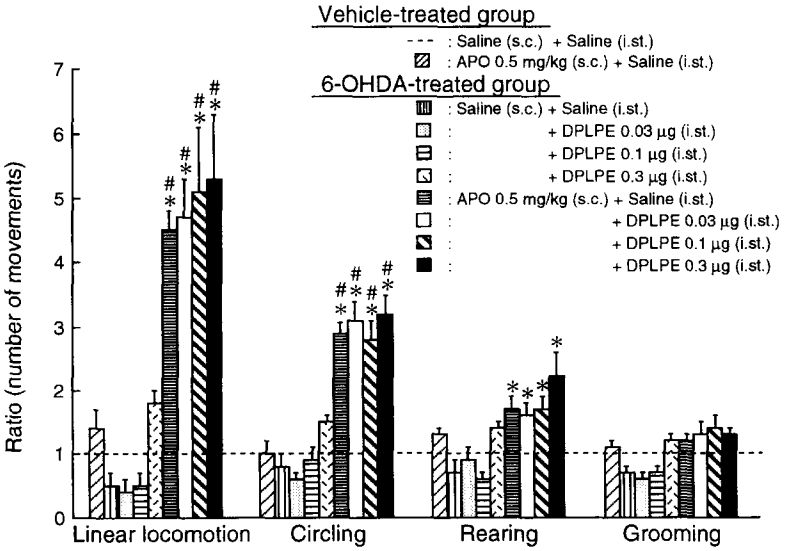

Fig. 3. Movements made by mice after the administration of apomorphine (APO) (0.5 mg/kg, s.c.), DPLPE (0.03, 0.1 and 0.3 μg, i.st.) and their combinations. Values represent the mean ± S.E. for 10 mice. * Denotes significant difference from vehicle control, $P < 0.05$. # Denotes significant difference from vehicle + APO (0.5 mg/kg, s.c.), $P < 0.05$.

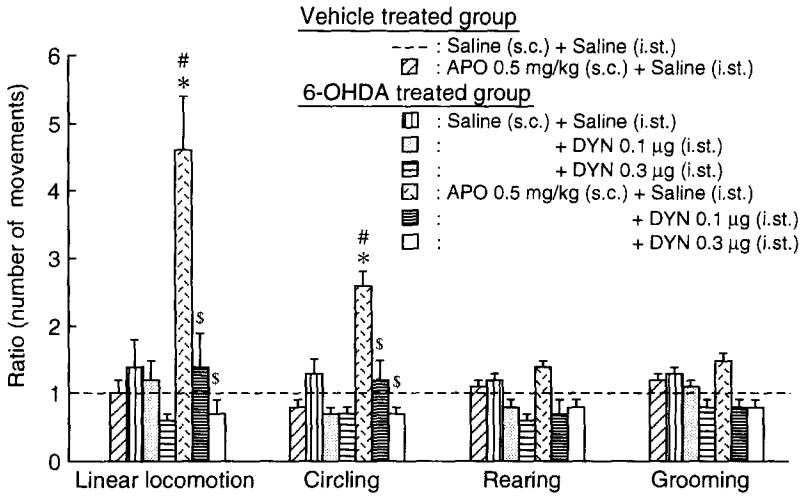

Fig. 4. Movements made by mice after the administration of apomorphine (APO) (0.5 mg/kg, s.c.), dynorphin A-(1–13) (DYN) (0.1 and 0.3 μg, i.st.) and their combinations. Values represent the mean ± S.E. for 10 mice. * Denotes significant difference from vehicle control, $P < 0.05$. # Denotes significant difference from vehicle + APO (0.5 mg/kg, s.c.), $P < 0.05$. $ Denotes significant difference from 6-hydroxydopamine (6-OHDA) + APO (0.5 mg/kg, s.c.), $P < 0.05$.

3.4. Effects of dynorphin A-(1–13)

ANOVA showed a significant relation of behavioral responses in vehicle- and 6-hydroxydopamine-treated groups ($P < 0.01$): $F(7,72) = 10.34$ for linear locomotion and $F(7,72) = 11.96$ for circling (Fig. 4). Dynorphin A-(1–13) (0.1 or 0.3 μg) had no significant effects on these behaviors, whereas a 0.5 mg/kg dose of apomorphine produced a marked increase in linear locomotion, contralateral circling and rearing in 6-hydroxydopamine-treated mice (Fig. 4). Dynorphin A-(1–13) (0.1 and 0.3 μg) almost completely inhibited the marked increase in behavior induced by apomorphine (0.5 mg/kg) (Fig. 4).

3.5. Effects of Mr2266 on the effects of dynorphin A-(1–13)

ANOVA revealed a significant relation of behavioral responses in vehicle- and 6-hydroxydopamine-treated groups ($P < 0.01$): $F(9,90) = 34.39$ for linear locomotion, $F(9,90) = 16.38$ for circling and $F(9,90) = 4.71$ for rearing (Fig. 5). Although Mr2266 (10 mg/kg)

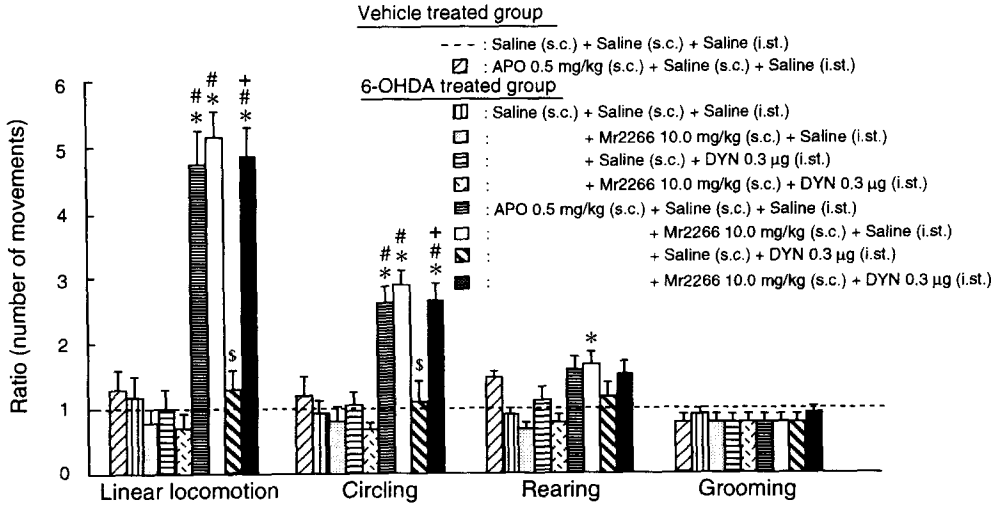

Fig. 5. Movements made by mice after the administration of apomorphine (APO) (0.5 mg/kg, s.c.), dynorphin A-(1–13) (DYN) (0.3 μg, i.st.), Mr2266 (10 mg/kg, s.c.) and their combinations. Values represent the mean ± S.E. for 10 mice. * Denotes significant difference from vehicle control, $P < 0.05$. # Denotes significant difference from vehicle + APO (0.5 mg/kg, s.c.), $P < 0.05$. $ Denotes significant difference from 6-hydroxydopamine (6-OHDA) + APO (0.5 mg/kg, s.c.), $P < 0.05$. + Denotes significant difference from 6-hydroxydopamine (6-OHDA) + APO (0.5 mg/kg, s.c.) + DYN (0.3 μg, i.st.), $P < 0.05$.

alone did not affect the behavioral patterns, the antagonistic effects of dynorphin A-(1–13) (0.3 μg) on the apomorphine (0.5 mg/kg)-induced behavioral responses were completely reversed by Mr2266 (10 mg/kg) (Fig. 5).

4. Discussion

Intracerebroventricular injections of DAMGO (0.003 and 0.01 μg, i.c.v.) (Ukai et al., 1991) and dynorphin A-(1–13) (10 μg, i.c.v.) (Ukai et al., 1989a) have been reported to inhibit the increase in rearing and/or grooming behavior induced by higher doses (0.56 and 1 mg/kg, s.c.) of apomorphine. The effects of DAMGO (0.01 μg, i.c.v.) and dynorphin A-(1–13) (10 μg, i.c.v.) are clearly reversed by receptor-selective opioid antagonists (Ukai et al., 1989a, 1991).

In the present study, intrastriatal injections of DAMGO (0.1 and 0.3 ng, i.st.) and dynorphin A-(1–13) (0.1 and 0.3 μg, i.st.) inhibited the marked increase in linear locomotion and contralateral circling induced by apomorphine (0.5 mg/kg, s.c.) in 6-hydroxydopamine-treated mice. The inhibitory effects of DAMGO (0.3 ng, i.st.) and dynorphin A-(1–13) (0.3 μg, i.st.) were fully reversed by the μ-selective opioid receptor antagonist β-funaltrexamine (5 μg, i.c.v.) and the κ-selective opioid receptor antagonist Mr2266 (10 mg/kg, s.c.), respectively. In contrast, DPLPE (0.03, 0.1 and 0.3 μg, i.st.) had no marked effects on the apomorphine (0.5 mg/kg, s.c.)-induced behavior in 6-hydroxydopamine-treated mice.

It is thus possible that the μ- and κ- but not δ-opioid receptor agonists played an inhibitory role in the behavioral sensitization induced by a low dose of apomorphine in 6-hydroxydopamine-treated mice as a result of the activation of postsynaptic sites of dopamine neurons, because the opioid receptor agonists used in this study have been reported to lack effects on hypomotility induced by a lower dose of apomorphine, which affects presynaptic sites of dopamine neurons (Ukai et al., 1993). In particular, the effects of DAMGO and dynorphin A-(1–13) seem to be associated with the function of dopamine D_2 receptors. For example, DAMGO (0.003 and 0.01 μg, i.c.v.) (Toyoshi et al., 1991) and dynorphin A-(1–13) (12.5 μg, i.c.v.) (Ukai et al., 1992) attenuate the dopamine D_2 receptor agonist RU 24213 (3 mg/kg, s.c.)-induced increase in behavioral responses, such as linear locomotion, circling, rearing and/or grooming, while these opioid receptor agonists have no significant effects on grooming behavior elicited by the dopamine D_1 receptor agonist SKF 38393 (10 mg/kg, s.c.) (Toyoshi et al., 1992; Ukai et al., 1992). In contrast, DPLPE (0.3, 1 or 1.75 μg, i.c.v.) has no significant effects on behavior induced by apomorphine (1 mg/kg, s.c.) (Ukai et al., 1992) or RU 24213 (3 mg/kg, s.c.) (Toyoshi et al., 1991), although the peptide (1 μg, i.c.v.) combined with SKF 38393 (10 mg/kg, s.c.) produces a marked increase in linear locomotion and circling (Toyoshi et al., 1992).

Furthermore, the effective dose (0.3 ng equivalent to 0.0006 nmol, i.st.) of DAMGO to attenuate the effects of apomorphine was lower than that of dynorphin A-(1–13) (0.3 μg equivalent to 0.187 nmol, i.st.), suggesting the key role of μ- rather than κ-opioid receptors in the apomorphine-induced behavioral responses. In addition, DAMGO did not just antagonize the apomorphine-induced behavior, but seemed to interact with the dopamine receptor agonist to elicit a greater than normal reduction in all behavioral responses. A similar effect was noted with dynorphin A-(1–13), which simply reduced the effects of apomorphine to control levels. It is thus likely that μ-opioid receptors close to dopamine neurons are sensitized by apomorphine in 6-hydroxydopamine-treated mice.

Apomorphine (1.0 mg/kg) produces a marked increase in grooming in normal mice (Ukai et al., 1989a), but a 0.5 mg/kg dose of apomorphine failed to produce a marked increase in grooming in mice injected with 6-hydroxydopamine into the striatum. Therefore, it is unlikely that the apomorphine-induced increase in grooming is mediated via the striatum.

There was a significant increase in rearing induced by apomorphine alone, while there was not an increase in other behaviors. Although not always significant, apomorphine produced a consistent increase in rearing.

In short, these findings suggest that one of the sites of action of DAMGO and dynorphin A-(1–13) for their inhibitory effects on dopamine-mediated behaviors is the striatum.

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