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Sex differences in the motor inhibitory and stimulatory role of dopamine D1 receptors in rats

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Abstract

We investigated sex differences in the motor responses to the full and selective dopamine D1-like receptor agonist, (±)-6-chloro-7,8-dihydroxyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrobromide (SKF-81297; 0.3, 3, and 10 mg/kg, s.c.), in non-habituated adult rats. In general, SKF-81297 produced a biphasic effect on motor activity (including locomotion, rearing and exploratory activity) which consisted of an initial short inhibition followed by a long-lasting stimulation. These effects were dose- and sex-dependent. The inhibitory phase was more pronounced in males than females while the opposite was true for the stimulatory phase. Importantly, the motor inhibitory effects of SKF-81297 were not due to an increase in stereotypy (e.g., grooming activity). These biphasic effects on several motor parameters suggest the presence of two distinct dopamine D1 receptor populations which have opposite effects on motor activity and which are, in part, sexually dimorphic. © 2002 Published by Elsevier Science B.V.

Keywords: Dopamine; Dopamine D1 receptor; SKF 81297; Motor activity; Grooming; Attention-deficit hyperactivity disorder

1. Introduction

Dopamine, a key neurotransmitter in the brain, exerts an important modulatory role in the control of motor activity, reward-related mechanisms, emotion and cognitive processes (Le Moal, 1995). Alterations in dopaminergic neurotransmission have been linked to various neuropsychiatric disorders, including Parkinson's disease, drug addiction, schizophrenia, attention-deficit/hyperactivity disorder, and Tourette's syndrome (Lyons et al., 1998; Wasilow-Mueller and Erickson, 2001; Reicher-Rossler and Hafner, 2000; Walters et al., 2001). There are clear clinical sex-associated differences (incidence, manifestation, treatment response) in these dopamine-related disorders which may indicate a sexual dimorphism in the organization of the dopamine system.

In the brain, the effects of dopamine are mediated via activation of two distinct families of receptors, referred to the D1 (D1 and D5) and the D2 (D2, D3, and D4) class (see Missale et al., 1998). These receptors exert their biological effects via G-protein-coupled intracellular signalling pathways and can be distinguished biochemically by their opposing action on adenylate cyclase. Dopamine receptors play a major role in the behavioural responses generated by psychoactive drugs. Such drugs include psychostimulants like amphetamine and cocaine, which are known to stimulate motor activity and produce addictive behaviour (Everitt et al., 2001). These drugs act centrally as indirect agonists rather than directly, by binding to receptor themselves. Interestingly, some of these psychostimulants (amphetamine and methylphenidate), when given therapeutically at low doses, can improve symptoms of attention-deficit/hyperactivity disorder (e.g., reduce symptoms of hyperactivity) (Solanto, 2000).

Dopamine D1 receptors are known to play an essential role in the motor effects of stimulants drugs (see Xu et al., 1994). Neuroanatomical studies have demonstrated that dopamine D1 receptors are localized postsynaptically (e.g., in the striatum, nucleus accumbens and olfactory tubercle) in relation to dopaminergic neurons (see Missale et al., 1998) and it is generally believed that they are linked to motor activity in a stimulatory fashion. Indeed, previous studies

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have reported increased motor activity after administration of several dopamine D1-like receptor agonists to normal rats (Molloy and Waddington, 1985; Abrahams et al., 1998; Cohen et al., 1999). However, all the above studies tested these compounds in rats which had been habituated to their testing conditions (i.e., creating a low baseline condition). Both human and experimental animal studies have demonstrated that drug-induced changes (e.g., stimulant drugs) in motor activity are highly dependent on the baseline activity of an individual (see Robbins, 2002). We therefore tested the hypothesis that under conditions of high baseline activity (i.e., non-habituated condition), administration of a dopamine D1 receptor agonist may also produce motor inhibition in normal rats. For this purpose, we investigated the motor responses to the full and selective dopamine D1-like receptor agonist, SKF-81297(0.3, 3, and 10 mg/kg s.c.), in non-habituated adult male and female rats. SKF 81297 was selected since it appears to a be highly selective dopamine D1 receptor ligand in vivo, based on its lack of inhibition of midbrain dopamine neurons (Ruskin et al., 1998) and its lack of response in dopamine D1 receptor-deficient mutant mice following systemic administration (Xu et al., 1994).

2. Materials and methods

2.1. Subjects

Adult male and female Sprague–Dawley rats (3 months old; BK Universal, Sollentuna, Sweden) were used. The animals arrived in the laboratory at least 1 week before experiments and were segregated by sex and housed in groups (four per cage, Makrolon IV) under controlled conditions of light/dark cycle (12:12 h, lights on at 0800 h). Food and tap water were available ad libitum. The experiments were approved by the local Committee on the Ethics of Animal Experimentation, Stockholm, Sweden. All experimental procedures complied with internationally approved standards for animal welfare.

2.2. Motor activity measurements

Motor activity (locomotion and rearing) was measured in two rats simultaneously by means of a multi-box ActiMot detection system (TSE, Germany). This system uses individual photocell activity units (48 × 48 cm) connected to a control unit. Each unit consisted of a base frame with two pairs of 16 light-barrier strips (transmitter and receiver), set at a distance of 14 mm, which are sensitive to infrared light. 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. The rats were monitored regularly via a screen monitor to confirm the results obtained for photocell interruptions of *Z*-coordinate light barriers, which reflected the number of rearing events.

A video camera was used to monitor grooming behaviour. Grooming was measured by the number of seconds that a rat spent engaged in facial strokes, paw licking, and body licking (see, Berridge and Aldridge, 2000).

2.3. Exploratory activity

A hole-board test was used to measure exploratory activity. A 16-hole-board frame was inserted into an individual photocell activity unit (see above). The number of hole visits was recorded on a computer. The rats were monitored regularly via a screen monitor to exclude the possibility of accidental beam interruptions due to the rat's tail.

2.4. Behavioural procedure

Testing took place between 1000 and 1700 h under dimmed light conditions. All experiments were carried out with non-habituated rats, which were used only once to avoid carry-over effects. Immediately after injection, each rat was placed in the centre of an activity box (novel environment). Data were collected at 5-min intervals over a period of 90 min.

2.5. Drug procedure

(±)-6-Chloro-7,8-dihydroxyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrobromide (SKF-81297; Research Biochemical and International, Natick, MA, USA) was dissolved in isotonic saline (0.9% NaCl) vehicle. The drug was freshly made for each trial. Subcutaneous (s.c.) injections were administered into the neck in doses of 0.3, 3.0, and 10 mg/kg in a vehicle volume of 1.0 ml/kg. The drug doses were calculated as salt weight.

2.6. Statistical analysis

All behavioural experiments (except grooming) were analysed using either repeated measures analysis of variance (ANOVA; treatment, sex and time as main factors) or factorial ANOVA. When ANOVA indicated a significant overall effect of treatment at $P < 0.05$ level, post-hoc testing was performed using Fisher's least significant difference (LSD) test. Grooming activity was analysed with Kruskall–Willis test. For all analyses, significance was assigned at the $P < 0.05$ or $P < 0.0001$ level.

3. Results

3.1. Effects of SKF-81297 on locomotor activity

The overall time course of the effects of SKF-81297 on the locomotor activity of male and female rats is presented in Fig. 1. ANOVA for repeated measures revealed signifi-

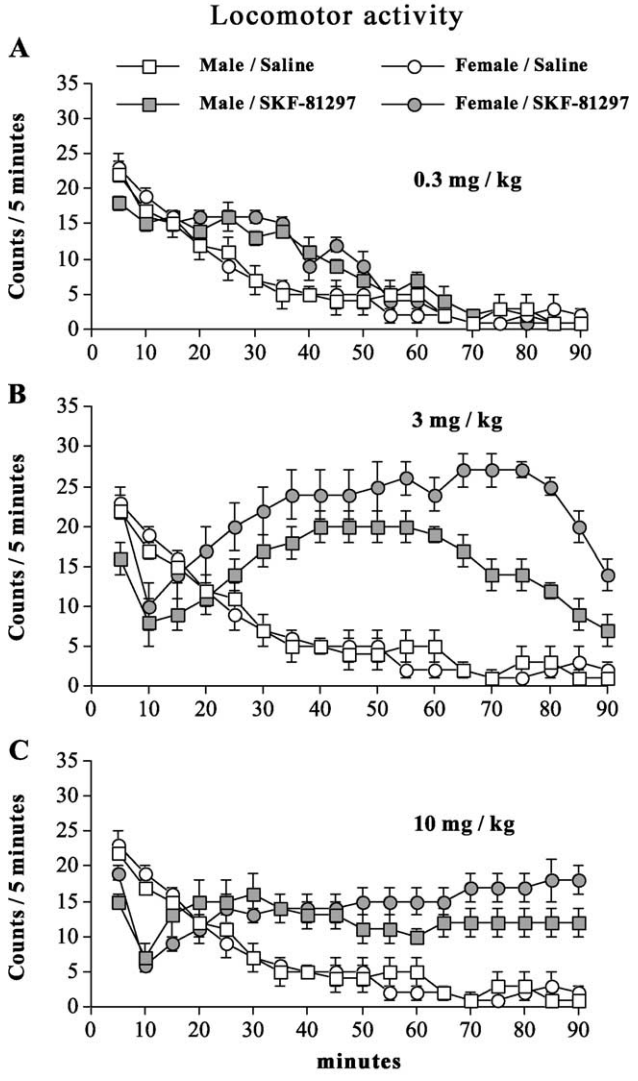

Fig. 1. The time course of the effects of SKF-81297 on locomotor activity in male and female rats (means of metres travelled ± S.E.M.; $n = 4–7$ and 8–12 per group for males and females, respectively). For further details, see Results.

cant DOSE [$F(3,51) = 34.553$, $P < 0.0001$], SEX [$F(1,51) = 6.129$, $P = 0.0167$], and TIME [$F(17,867) = 34.114$, $P < 0.001$] main effects of SKF-81297 on the locomotor activity as well as a significant DOSE × TIME interaction [$F(51,867) = 24.885$, $P < 0.001$]. In addition, there were significant TIME × SEX [$F(17,867) = 1.985$, $P = 0.0101$] and DOSE × SEX × TIME [$F(51,867) = 1.768$, $P = 0.001$] interactions. In general, SKF-81297 had an initial inhibitory effect (5–15 min after injection) and a later stimulatory effect (25–90 min) on locomotor activity (see Fig. 1).

Separate ANOVAs for each time point revealed significant DOSE effects at the 5 min ($P = 0.0169$), 10 min ($P < 0.0001$), and 15 min ($P = 0.0389$) time points and during the 25- to 90-min interval ($P < 0.0001$). Significant SEX effects were observed at the 5-, 50-, 60-, and 65-min time points ($P < 0.05$), the 70-min time point ($P < 0.0001$), and during the 75- to 90-min interval ($P < 0.05$). In addition, a significant DOSE × SEX interaction was observed during the 55- to 65-min interval ($P < 0.05$), the 70- to the 75-min interval ($P < 0.0001$), and the 80- to 85-min interval ($P < 0.05$).

Separate ANOVAs for each sex at the first 5-min time point revealed significant DOSE effects of SKF-81297 in male rats [$F(3,19) = 7.292$, $P = 0.0019$], whereas the effects in female rats failed to achieve significance [$F(3,32) = 1.344$, $P = 0.2775$]. Further post-hoc analysis with Fisher's LSD test showed that all doses (0.3, 3, and 10 mg/kg) of SKF-81297 produced significant decreases (with respect to the vehicle-injected control group) in locomotor activity in males at this time point ($P < 0.05$). Thus, at the first 5-min time point, males were more sensitive to the inhibitory effects of SKF-81297 than females.

In order to determine whether female rats were more sensitive to the stimulatory effects of the drug (as suggested by visual inspection of Fig. 1), we performed a factorial ANOVA (with SEX and DOSE as main factors) using the accumulated data for the 50- to 90-min interval (see above for statistical details). Factorial ANOVA showed significant DOSE [$F(3,51) = 92.923$, $P < 0.0001$] and SEX [$F(1,51) = 12.202$, $P < 0.0001$] effects of SKF-81297 on locomotor activity, as well as a significant DOSE × SEX interaction [$F(3,51) = 7.710$, $P = 0.0002$]. Further post-hoc analysis with Fisher's LSD test showed that the 3 and 10 mg/kg doses of SKF-81297 significantly ($P < 0.01$) increased locomotor activity in both sexes (with respect to their respective vehicle-injected control groups). However, females showed significantly ($P < 0.05$) higher counts than males (26 ± 8, 214 ± 13, 147 ± 18 versus 20 ± 4, 132 ± 13, 105 ± 14 for isotonic saline vehicle, 3 and 10 mg/kg of SKF-81297, respectively). Thus, during the 50- to 90-min interval females were more sensitive to the stimulatory effects of SKF-81297 than males.

3.2. Effects of SKF-81297 on the number of rears

For the sake of clarity, the overall time course of the effects of SKF-81297 on the number of rears is presented in Figs. 2 and 3, for males and females, respectively. ANOVA for repeated measures revealed significant DOSE [$F(3,51) = 13.424$, $P < 0.0001$] and TIME [$F(17,867) = 26.754$, $P < 0.001$] main effects of SKF-81297 on the number of rears as well as a significant DOSE × TIME interaction [$F(51,867) = 13.777$, $P < 0.001$]. In addition, there were significant DOSE × SEX [$F(3,51) = 9.448$, $P < 0.001$] and TIME × SEX [$F(17,867) = 2.674$, $P = 0.0003$] interactions. In general, SKF-81297 induced a dose-dependent reduction in rearing activity in males (see Fig. 1) while in females this effect was less pronounced, especially at the 0.3 and 3 mg/kg doses (see Fig. 2).

Separate ANOVAs for each time point revealed significant DOSE effects during the 5- to 15-min ($P < 0.0001$), 20- to 45-min ($P < 0.005$), and 55- to 90-min intervals

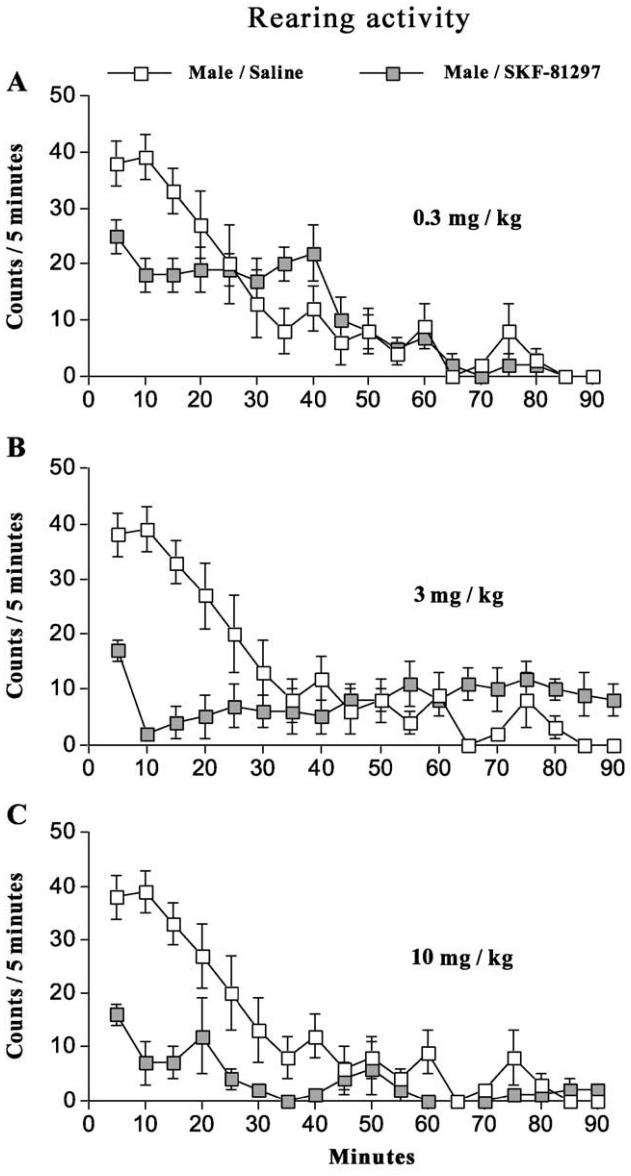

Fig. 2. The time course of the effects of SKF-81297 on the number of rears in males (means ± S.E.M.; $n = 4–7$ per group). For further details, see Results.

($P < 0.0001$). Significant SEX effects were observed during the 65- to 90-min interval ($P < 0.05$) as well as a significant DOSE × SEX interaction at the 20 min ($P < 0.05$), 55 min ($P < 0.05$), and 60 min ($P < 0.05$) time points as well as during the 65- to 80-min interval ($P < 0.0001$), and at the 85-min time point ($P < 0.05$).

Separate analyses for each sex revealed that in males all doses (0.3, 3, and 10 mg/kg) of SKF-81297 significantly decreased activity (with respect to the vehicle-injected group) during the 5- to 15-min interval ($P < 0.05$, $P < 0.001$, $P < 0.001$, respectively), as well as at the 20-min time point in the case of the 3 mg/kg dose ($P < 0.001$). The 0.3 mg/kg dose significantly increased activity (with respect to the vehicle-injected group) at the 35-min time point ($P < 0.05$) and the 3 mg/kg dose at the 65-, 70-, 80-, 85-, and 90-min time points ($P < 0.05$). In females, the 0.3 mg/kg dose of SKF-81297 significantly increased activity (with respect to the vehicle-injected group) during the 30- to 40-min interval ($P < 0.05$). The 3 and 10 mg/kg doses significantly decreased activity (with respect to the vehicle-injected group) at the 5- and 10-min time points ($P < 0.05$ and $P < 0.001$, respectively). In addition, the 3 mg/kg dose increased activity at the 45- and 50-min time points ($P < 0.05$) and during the 50- to 90-min interval ($P < 0.001$). Thus, it is clear that during the first 5- to 15-min males were more sensitive to the inhibitory effects of the drug than females.

In order to determine whether females were more sensitive to the stimulatory effects of the drug (as suggested by visual inspection of Figs. 2 and 3), we performed an ANOVA (with SEX and DOSE as main factors) using the

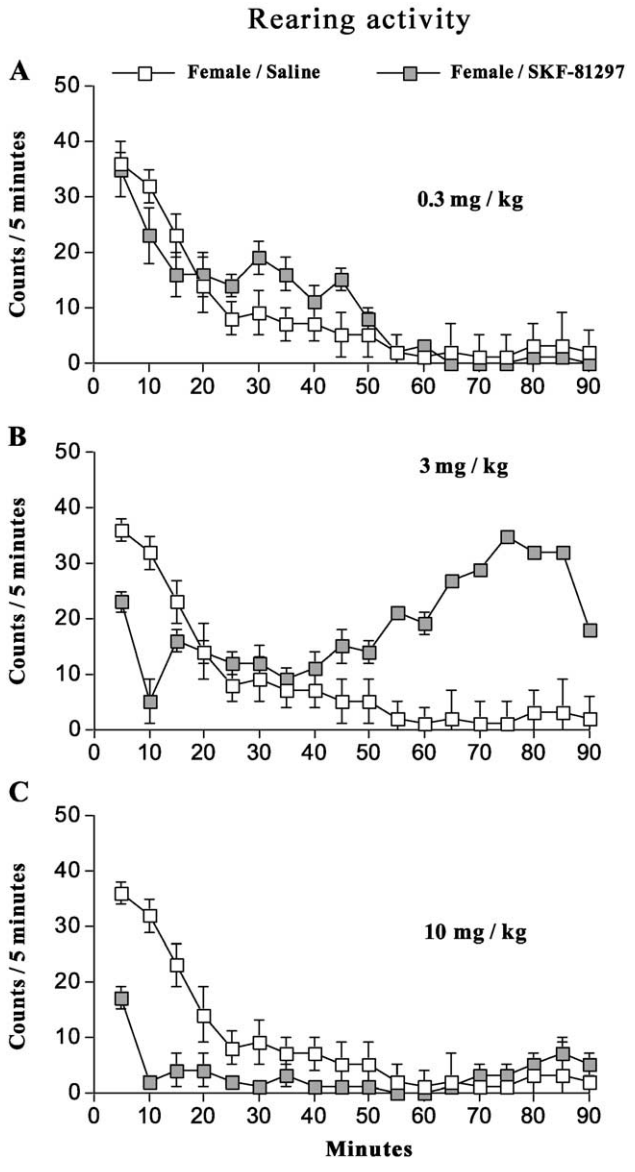

Fig. 3. The time course of the effects of SKF-81297 on the number of rears in females (means ± S.E.M.; $n = 8–12$ per group). For further details, see Results.

accumulated data from the 65- to 90-min interval (see above). ANOVA revealed a significant DOSE [$F(3,51) = 51, 406$, $P < 0.0001$] and SEX [$F(1,51) = 17.026$ $P < 0.0001$] effect of SKF-81297 on the number of rears as well as a significant DOSE × SEX interaction [$F(3,51) = 13,705$ $P < 0.0001$]. Further post-hoc analysis with Fisher's LSD test showed that the 3 mg/kg doses of SKF-81297 significantly increased activity in both sexes (with respect to their respective vehicle-injected groups). However, females showed significantly ($P < 0.05$) higher counts than males (12 ± 5, 174 ± 20 versus 12 ± 8, 61 ± 14, respectively). Thus, during the above intervals, females were more sensitive to the stimulatory effects of SKF-81297 than males.

3.3. Effects of SKF-81297 on grooming activity

The effects of SKF-81297 on grooming activity were examined during the first 15-min after SKF-81297 or vehicle administration. The results are presented in Table 1. SKF-81297 had a significant dose effect ($P < 0.001$) on time spent grooming. Both the intermediate and high doses (3 and 10 mg/kg) of SKF-81297 decreased time spent grooming in both sexes. The apparent increase in grooming in males receiving the lower dose (0.3 mg/kg) did not achieve statistical significance.

3.4. Exploratory activity

The number of hole visits was recorded for 60 min. ANOVA for repeated measures revealed significant DOSE [$F(2,54) = 28.719$, $P < 0.0001$], TIME [$F(11,594) = 23.992$, $P < 0.001$], and SEX [$F(2,54) = 4.999$, $P = 0.0295$] effects of SKF-81297 on exploratory activity. In addition, there was a significant DOSE X TIME interaction [$F(22,594) = 8.673$, $P < 0.0001$].

Based upon the statistical analysis of the time course of the SKF-81297 effects on the number of hole visits (data not shown), the data from the 0- to 15-min (Fig. 4A) and the 25- to 60-min intervals (Fig. 4B) were combined and used for analysis. The 0.3 mg/kg dose of SKF-81297 significantly decreased the number of hole visits during the 0- to 15-min interval (Fig. 4A) but increased it during the 25- to 60-min interval (Fig. 4B). In contrast, the 3 mg/kg dose decreased the number of hole visits during both intervals. No sex differences were found.

Table 1
Effects of SKF-81297 on time spent grooming

Groups	Males	Females
Vehicle	70 ± 20	93 ± 13
SKF (0.3 mg/kg)	112 ± 17	99 ± 13
SKF (3 mg/kg)	3 ± 3^{b}	3 ± 1^{a}
SKF (10 mg/kg)	1 ± 1^{b}	1 ± 1^{b}

The time spent grooming is shown as accumulated seconds during the 15-min interval after SKF (0.3, 3, and 10 mg/kg) or vehicle administration. The results are presented as means ± S.E.M. ($n = 6-9$ and $4-7$ per group, for females and males, respectively). Significant differences from the vehicle group of the same sex are shown: $^{a}P < 0.05$, $^{b}P < 0.001$.

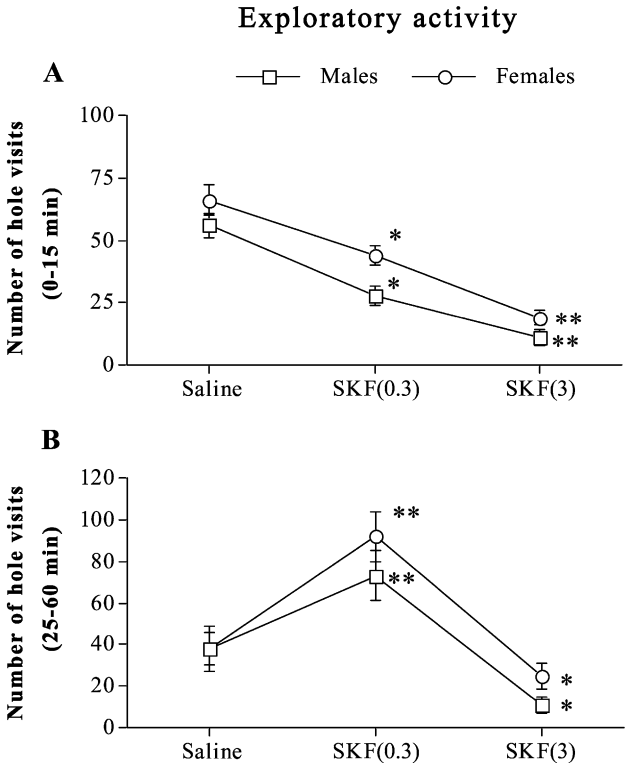

Fig. 4. The effects of SKF-81297 on the number of hole visits of male and female rats. The accumulated counts for the 0- to 15-min (A) and 25- to 60-min (B) intervals after SKF-81297 or saline injection (means ± S.E.M.; $n = 6-11$ and $11-12$/group, for males and females, respectively). Significant differences from saline (vehicle-injected) group of the same sex are shown: $^{*}P < 0.05$, $^{**}P < 0.001$.

4. Discussion

4.1. General evaluation

The main finding of this study was that SKF-81297, a selective and full dopamine D1-like receptor agonist, exerted both inhibitory and stimulatory motor effects in adult rats. These effects were found to be sex-dependent. These biphasic effects on several motor parameters suggest the presence of two distinct dopamine D1 receptor populations which have opposing effects on motor activity and which are, in part, sexually dimorphic.

4.2. Effects of SKF-81297 on motor activity: comparison with previous studies

Previous investigations have reported increased motor activity (locomotor and rearing activity) after administration of several dopamine D1-like receptor agonists in rats, including *R*(+)-1-phenyl-2,3,4,5-tetrahydro-(1*H*)-3-benzazepine-7,8-diol (SKF-38393), (±)-*N*-allyl-6-chloro-2,3,4,5-tetra-

hydro-7,8-dihydroxy-1-phenyl-1*H*-3-benzazepine hydrobromide (SKF-82958) and SKF-81297 (Molloy and Waddington, 1985; Abrahams et al., 1998; Cohen et al., 1999). The present results confirm and extend these findings. Increased locomotor activity was observed after administration of SKF-81297 in both sexes. However, this effect was preceded by a short but significant suppression of locomotor activity. This inhibitory effect was not due to an increase in stereotypy (i.e., grooming) because time spent grooming was reduced at doses which reduced locomotor activity. Interestingly, males were more sensitive to the locomotor inhibitory effect of SKF-81297 than females whereas the later hyperactive response was greater in females.

We also found a clear dose-dependent inhibition of rearing activity after administration of SKF-81297 in males. This effect was less pronounced in females, especially at the 0.3 and 3 mg/kg doses. One interesting aspect of the response to SKF-81297 was the lack of sex difference in exploratory activity, despite clear sex differences in locomotor and rearing activity. These findings argue against sex differences in the metabolism and/or absorption of SKF-81297 as the principal explanation for the sex-associated effects on locomotion and rearing. Moreover, our data demonstrated a dissociation between the effects of SKF-81297 on rearing activity and inquisitive exploratory activity (i.e., hole visits), suggesting the involvement of different neuronal substrates.

In the above-mentioned previous studies, the full dopamine D1-like receptor agonists were tested in habituated rats while the rats in our study were not habituated. Recently, Salmi and Ahlenius (2000) reported that (1*R*,3*S*)-1-aminomethyl-5,6-dihydroxy-3-phenylisochroman HCl (A 68930), a full and selective dopamine D1-like receptor agonist, produced sedative effects on the spontaneous locomotor activity of male rats in an open-field test. Taken together, it appears that the motor inhibitory effects of dopamine D1-like receptors are only revealed during high baseline activity (e.g., under novel conditions) in rats.

4.3. Effects of SKF-81297 on grooming: comparison with previous studies

Grooming behaviour in rodents has long been associated with dopamine D1 receptors in the brain. Thus, peripheral administration of dopamine D1-like receptor agonists (i.e., SKF-38393) elicits grooming behaviour which can be selectively blocked by pretreatment with a dopamine D1-like receptor antagonist (i.e., SCH23390; *R*(+)-7-chloro-8-hydroxy-1phenyl-2,3,4,5,-tetrahydro-1*H*-benzazepine HCl) (Molloy and Waddington, 1984). Moreover, dopamine D1 receptor mutant mice but not dopamine D2 receptor mutant mice show clear impairments in novelty-induced grooming (Drago et al., 1999). In the present study, grooming behaviour was induced in males by the lower dose (0.3 mg/kg) of SKF-81297, similar to that previously reported (Cohen et al., 1999). However, at higher doses (3 and 10 mg/kg) of SKF-81297, we found that grooming behaviour was inhibited during the first 15 min after drug administration. More recently, Berridge and Aldridge (2000) reported the effects of another full dopamine D1-like receptor agonist (SKF-82958). These authors found that peripheral administration of certain doses of SKF-82958 decreased the percentage of time spent grooming. One explanation for the apparent discrepancy between the behavioural effects of SKF-38393, SKF-81297 and SKF-82958 may be that SKF-38393 is only a partial dopamine D1-like receptor agonist, stimulating adenylate cyclase activity less than dopamine itself, whereas SKF-81297 and SKF-82958 are full dopamine D1-like receptor agonists (Andersen and Jansen, 1990).

4.4. Stimulatory effects of SFK-81297: potential role of the striatum

Several findings indicate that the stimulatory effects of SKF-81297 are mediated via activation of striatal dopamine D1 receptors. Clinical studies have long recognized the importance of the striatum and other basal ganglia nuclei in movement (Bathia and Marsden, 1994). In rodents, the meso-striatal and meso-limbic dopaminergic pathways are known to participate in the control of spontaneous and dopamine receptor-mediated motor activity (see Le Moal, 1995). In particular, descending influences from the nucleus accumbens via the ventral pallidum to the mesencephalic locomotor region provide a link between limbic and motor regions (Mogenson, 1991). Neuroanatomical studies have demonstrated that dopamine D1 receptors are highly expressed in the striatum, nucleus accumbens and olfactory tubercle, with somewhat lower concentrations in the frontal cortex (see Missale et al., 1998). Peripheral administration of a dopamine D1-like receptor agonist is known to induce a robust expression of immediate early genes (e.g., c-Fos) in the normal rat striatum, especially in the nucleus accumbens, olfactory tubercle and cerebral cortex (Wang and McGinty, 1996). This induction of striatal immediate early genes occurs only in medium-sized spiny neurons and can be dose-dependently correlated with increases in motor activity. Moreover, bilateral intra-accumbal injection of SKF-38393 induces a dose-related increase in motor activity (Dreher and Jackson, 1989). Recent molecular studies indicate that the stimulatory effects of SKF-81297 are mainly mediated by the activation of the dopamine D1 receptor, probably located in the ventral striatum (Xu et al., 1994; Holmes et al., 2001).

4.5. Inhibitory effects of SFK-81297: potential role of the medial prefrontal cortex

Several lines of evidence suggest that the medial prefrontal cortex is a possible neuronal substrate mediating the inhibitory effects of SKF-81297 on locomotor activity, as observed in the present study. For example, ibotenic acid lesions of the medial prefrontal cortex are known to increase

the behavioural responses to various dopamine agonists, including SKF-38393 (Braun et al., 1993). Moreover, intramedial prefrontal cortex injections of the dopamine D1 receptor antagonist SCH-23390, but not of other dopamine receptor antagonists, enhance the locomotion induced by intra-nucleus accumbens injection of amphetamine (Vezina et al., 1991). In addition, molecular studies have demonstrated that administration of SKF-81297 reduces locomotor activity in transgenic mice overexpressing the dopamine D1 receptor in extrastriatal areas, including the medial prefrontal cortex, while in wild-type mice it enhances locomotion (Dracheva et al., 1999).

Alternatively, the inhibitory effects of SKF-81297 on locomotor activity could be mediated by a subpopulation of inhibitory dopamine D1-like receptors within the ventral striatum (see above). Future studies are required to determine the localization of these inhibitory receptors.

4.6. Potential role of D5 receptors in the effects of SKF-81297

The dopamine D5 receptor subtype of the dopamine D1 family of receptors shares a high sequence homology and pharmacological profile with the dopamine D1 receptor subtype (see Missale et al., 1998) and, therefore, could contribute to the behavioural effects of SKF-81297. Recent studies indicate that the dopamine D5 receptor may make only a small contribution to the effects of SKF-81297 in vivo. Thus, the hyperactivity-inducing effects of SKF-81297 were only mildly attenuated in dopamine D5 receptor mutant mice (Holmes et al., 2001). In addition, the hypoactivity-inducing effects of the dopamine D1-like receptor antagonist, SCH-23390, were unaffected in dopamine D5 receptor mutant mice. Moreover, dopamine D5 receptor mutant mice were found to be generally normal in a range of tasks, including locomotor activity and motor coordination. Further studies are required to test the possibility that under certain pathological conditions (e.g., altered presynaptic dopamine tone) the dopamine D5 receptor may act to depress or inhibit motor activity (see Dziewczapolski et al., 1998).

4.7. Conclusions

In conclusion, the present study provides evidence of sex differences in the motor inhibitory and stimulatory role of dopamine D1 receptors in rats and suggests the presence of two distinct dopamine D1 receptor populations in the brain. Importantly, it appears that the motor inhibitory effects of dopamine D1 receptors are only revealed under high baseline activity. Sex differences in the prevalence, onset and course of dopamine-linked neurodevelopmental disorders could arise, in part, from developmental differences in these two distinct dopamine D1 receptor populations. The results may also help to explain the ''calming effects'' of stimulant medications (i.e., methylphenidate and D-amphetamine) in children with attention-deficit/hyperactivity disorder (see Robbins, 2002). Dopamine D1 receptors are known to play a major role in the postsynaptic effects of psychostimulants. Potential developmental disturbances in the balance between these two distinct dopamine D1 receptor populations in these children (who have high baseline motor activity) may explain why they show a greater reduction in activity after stimulant medication when compared to normal children and adults (see Robbins, 2002).

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