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European Journal of Pharmacology 365 (1999) 125–131

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The expression of neuropeptide-induced excessive grooming behavior in dopamine D_1 and D_2 receptor-deficient mice

Filippo Drago [a,*], Angelo Contarino [b], Lina Busà [a]

[a] *Institute of Pharmacology, University of Catania Medical School, Viale A. Doria 6, 95125 Catania, Italy*
[b] *Department of Neuropharmacology, The Scripps Research Institute, 10550 North Torrey Pines Rd., La Jolla, CA, USA*

Received 23 July 1998; revised 6 November 1998; accepted 24 November 1998

Abstract

Grooming behavior in rodents has long been related to dopamine receptors in the brain. However, the relative contribution of dopamine D_1-like receptors (D_1 and D_5) and D_2-like receptors (D_2, D_3 and D_4) in this behavior has not been established yet. Spontaneous novelty-induced grooming (as assessed with a 30-min sampling test) was reduced in knockout mice lacking the dopamine D_1 receptor. Furthermore, the intracerebroventricular (i.c.v.) injection of small quantities of oxytocin, prolactin or the adrenocorticotrophic hormone 1-24 fragment, ACTH-(1-24) was followed by a diminished level of novelty-induced excessive grooming. These neuropeptides caused a sustained increase in grooming level of control animals (wild type). Interestingly, the i.c.v. injection of β-endorphin enhanced novelty-induced grooming to a level similar in control and knockout mice. The systemic administration of the dopamine D_2 receptor antagonist, sulpiride did not suppress the residual grooming activity shown by animals injected with oxytocin, prolactin or ACTH-(1-24), and did not change the behavioral expression of those injected with β-endorphin. In contrast, the systemic administration of the opioid receptor antagonist, naloxone, totally suppressed the residual grooming activity of oxytocin-, prolactin- or ACTH-(1-24)-injected mice and of those treated with β-endorphin. In contrast with the behavioral deficit observed in dopamine D_1 receptor-deficient mice, dopamine D_2 receptor-null animals showed a normal expression of spontaneous novelty-induced grooming and a high level of grooming activity induced by i.c.v. injection of oxytocin, prolactin, ACTH-(1-24) or β-endorphin. Again, the peripheral injection of naloxone was followed by a suppression of neuropeptide-induced excessive grooming in these animals. These data suggest that dopamine D_1 receptors are involved in the expression of novelty-induced grooming in mice. In contrast, dopamine D_2 receptors seem not to be important for the expression of this behavior. Furthermore, neuropeptide-enhanced grooming involves dopamine D_1, but not dopamine D_2 receptors. However, neurotransmitters other than dopamine (e.g., endorphins) may play a supplementary role in neuropeptide-enhanced grooming in mice.

Keywords: Grooming; Dopamine receptor; Oxytocin; Prolactin; ACTH-(1-24) (adrenocorticotrophic hormone-(1-24); β-Endorphin

1. Introduction

Grooming is a 'maintenance' behavior, a common species-characteristic movement pattern with readily definable components (Bolles, 1960; Fentress, 1973). In rodents, spontaneous grooming behavior may occupy as much as 25%–40% of the awake time, but is specifically elicited in situations in which an animal is in stress-induced conflict or frustration. A typical condition of such type is novelty-induced grooming. Under this situation, grooming may play a deactivating role in restoring homeostasis (Gispen and Isaacson, 1981). Different neuropeptides, related or not to stress, may stimulate novelty-induced grooming: adrenocorticotrophic hormone (ACTH) and related neuropeptides (Gispen et al., 1975), β-endorphin (Gispen et al., 1976), prolactin (Drago et al., 1980), oxytocin and related neuropeptides (Drago et al., 1986a; Caldwell et al., 1986). Although the behavioral element analysis revealed that grooming may be different, all these neuropeptides act at least in part through the facilitation of dopamine neurotransmission in the brain (Drago et al., 1981a; Gispen and Isaacson, 1981; Drago et al., 1986a; Pedersen et al., 1988). Opioid neurotransmission may also be involved in the behavioral effect of

* Corresponding author. Tel.: +39-95-330709; Fax: +39-95-333219; E-mail: fdrago@tin.it

0014-2999/99/$ - see front matter
PII: S0014-2999(98)00877-2

neuropeptides (Gispen and Isaacson, 1981; Drago, 1988; Pedersen et al., 1988).

Although grooming behavior in rodents has long been related to dopamine receptors in the brain, the relative contribution of dopamine D_1-like receptors (D_1 and D_5) and D_2-like receptors (D_2, D_3 and D_4) in this behavior has not been established yet. The dopamine neurotransmission in the striatum and/or in nucleus accumbens seems to play a role in neuropeptide-induced excessive grooming (Gispen and Isaacson, 1981; Drago et al., 1981a, 1984, 1986b). Acute administration of psychomotor stimulants such as amphetamine or cocaine results in behavioral activation, including enhancement of grooming (Breese et al., 1987; Tella, 1994). In contrast, the use of non-selective dopamine receptor antagonists reduce or totally abolishes novelty-induced grooming and neuropeptide-induced excessive grooming in rats (Gispen and Isaacson, 1981; Drago et al., 1981a; Drago, 1988).

Mutant mice lacking functional dopamine D_1 receptors show various behavioral alterations. The most striking behavioral abnormality found in dopamine D_1 receptor-null mice is a drastic reduction of rearing behavior (Drago et al., 1994) that is not stimulated by acute injection of cocaine (Xu et al., 1994a; Drago et al., 1996). These animals also fail to show cocaine-induced stimulation of locomotor activity (Drago et al., 1996). In fact, while pharmacological studies have shown that rearing may be stimulated or suppressed by selective dopamine D_1 receptor agonists or antagonists, respectively (Hoffman and Beninger, 1985; Meyer et al., 1993), other behaviors may be influenced by such a drug action. In dopamine D_1 receptor-deficient mice, spontaneous grooming and sniffing are not eliminated, and locomotor activity may not be decreased (Drago et al., 1996). In the present study, dopamine D_1 receptor- and dopamine D_2 receptor-deficient mice were used to investigate whether novelty-induced grooming and neuropeptide-induced excessive grooming are critically dependent on these receptors. For this purpose, novelty-induced grooming was triggered in these animals by injection neuropeptides, such as ACTH, prolactin, oxytocin and β-endorphin.

2. Materials and methods

2.1. Animals

Male homozygous recombinant mice were generated by breeding heterozygous mutant mice pairs. Mice were routinely back-crossed to ensure homogeneity of the population. Half the mice were homozygous for the dopamine D_1 receptor or dopamine D_2 receptor gene deletion ($-/-$), while the other half were normal controls ($+/+$). The initial breeding pairs were obtained from the original breeding colony established at the National Institute of Health, Bethesda, MD, USA. Ten to 15-week-old mice were used.

Animals were bred under standard animal housing conditions, in a 12 h light/dark cycle (lights on between 8:00 and 20:00). Commercial animal food and tap water were available ad libitum. All experiments were conducted blind to treatment in conformity with the European Communities Council Directive 86/609/EEC.

2.2. Drug treatment

A week after habituation in the facilities, all animals were admitted to experimental procedures. They were injected intracerebroventricularly (i.c.v.) using a standard free-hands procedure (insertion of a 5 μl Hamilton syringe into the third ventricle) with 5 ng oxytocin (Cys–Tyr–Ile–Gln–Asn–Cys–Pro–Leu–Gly–NH_2 acetate salt, Sigma, USA), 10 ng prolactin (rat prolactin, NIH), 10 ng ACTH 1-24 fragment [ACTH-(1-24), Organon, The Netherlands] or 2 ng β-endorphin (Sigma). Neuropeptides were freshly dissolved in saline and injected in a total volume of 1 μl. At the end of experimental procedures, all animals were sacrificed by decapitation and the exact site of injection was checked by histological examination. All animals appeared to be correctly injected and hence data of all of them were included in the statistical analysis.

In some experiments, the dopamine D_2 receptor antagonist, sulpiride (Janssen, Italy) or the opioid receptor antagonist, naloxone (Sigma) were dissolved in saline and injected i.p. at the dose of 5 mg/kg and 2 mg/kg, respectively. It should be noted that these doses are in the range of those used in other experiments on neuropeptide-enhanced grooming (Gispen and Wiegant, 1976; Gispen et al., 1976; Wiegant et al., 1978; Gispen and Isaacson, 1981; Pedersen et al., 1988; Drago, 1988).

A group of mice injected with saline in the same volume and by the same route of the active groups was included in all experiments.

2.3. Behavioral test

Novelty-induced grooming behavior was observed between 15:00 and 18:00 h, under the same environmental conditions according to the original method described by Gispen et al. (1975). The mice were placed individually into plexiglas boxes ($24 \times 12 \times 24$ cm) in a low noise room. After a minute of adaptation, the behavior of the animals was sampled every 15 s, and the occurrence of grooming was recorded in a session of 30 min. The occurrence of the following single elements of grooming was scored as grooming: washing (vibrating movements of the fore paws in front of the snout and liking of the same paws leading to a series of strokes along the snout and semicircular movements over the top of the head), scratching (scratching of the body by one of the limbs), licking (licking of the body fur, limbs and tail), and genital

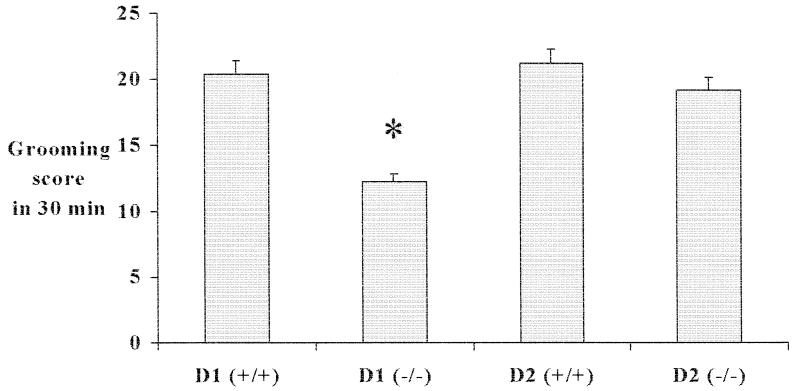

Fig. 1. The expression of novelty-induced grooming in dopamine D_1 receptor-deficient $(-/-)$ or D_2 receptor-deficient $(-/-)$ mice as compared to their littermates $(+/+)$. Behavioral measure was made with a 30-min sampling test in animals exposed to a novel environment. Values are mean ± S.E.M. Two-way ANOVA revealed a significant effect of genotype $[F(3,27) = 5.35,\ P < 0.01]$. * Significant difference vs. normal $(+/+)$ controls ($P < 0.01$, Dunnett's test for multiple comparisons).

grooming (licking of genital area). Stretching and yawning episodes were not recorded.

Grooming behavior of all animals was recorded on a tape using a videocamera (Philips Videocam) and then scored in monitor display by two independent observers. The mean score of the two observations was used for the statistical analysis.

All experimental groups of each genotype were composed of 7 mice. In summary, mice were injected i.c.v. with saline, oxytocin, prolactin, ACTH-(1-24) or β-endorphin and observed 30 min later. When sulpiride or naloxone were used, these drugs were injected i.p. 30 min prior to neuropeptides.

2.4. Statistical analysis

The two-way analysis of variance (two-way ANOVA) followed by the post-hoc Dunnett test for multiple comparisons were used for the statistical analysis of data. A P level of 0.05 or less was accepted as indicative of a significant difference.

3. Results

Fig. 1 shows the magnitude of novelty-induced grooming in dopamine D_1 receptor- and dopamine D_2 receptor-deficient $(-/-)$ mice compared to normal controls $(+/+)$. Null genotype for dopamine D_1 receptor was accompanied by a significant decrease in novelty-induced grooming [significant effect of genotype ($P < 0.01$)]. This behavior was, however, not totally abolished in dopamine D_1 receptor-null animals. In contrast, dopamine D_2 receptor-deficient mice showed a normal level of novelty-induced grooming.

Small quantities of neuropeptides injected i.c.v. potently stimulated novelty-induced grooming in normal mice (Fig. 2). Dopamine D_1 receptor-deficient mice that showed a

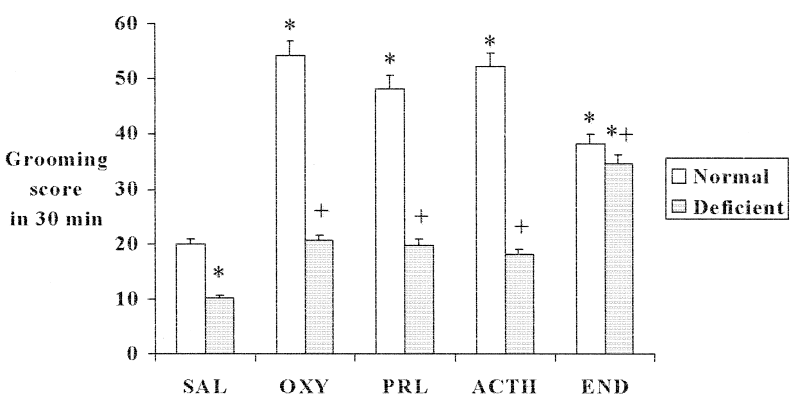

Fig. 2. The expression of excessive grooming induced in dopamine D_1 receptor-deficient mice by i.c.v. injection of neuropeptides made 30 min prior to behavioral testing. Doses of neuropeptides were: 5 ng for oxytocin, 10 ng for prolactin, 10 ng for ACTH-(1-24), and 2 ng for β-endorphin. Values are mean ± S.E.M. Two-way ANOVA revealed a significant effect of treatment $[F(4,34) = 5.12,\ P < 0.01)]$ and genotype $[F(4,34) = 4.89,\ P < 0.05)]$. * Significant difference vs. saline-injected normal $(+/+)$ controls ($P < 0.01$, Dunnett's test for multiple comparisons). + Significant difference vs. saline-injected dopamine D_1 receptor-deficient $(-/-)$ animals ($P < 0.01$, Dunnett's test for multiple comparisons).

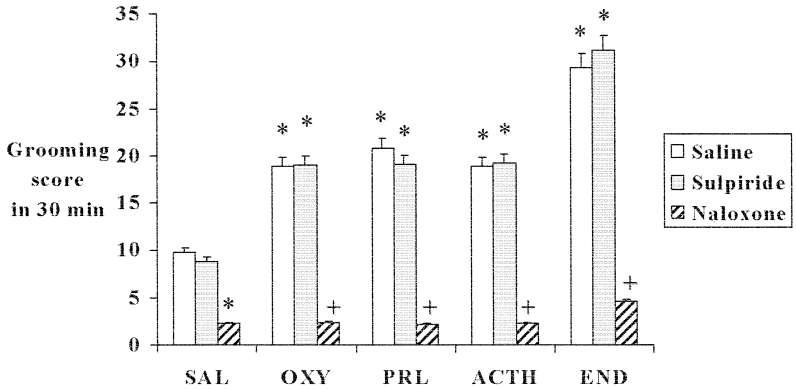

Fig. 3. The effect of sulpiride or naloxone on the expression of excessive grooming induced in dopamine D_1 receptor-deficient mice by i.c.v. injection of neuropeptides. Values are mean ± S.E.M. Two-way ANOVA revealed a significant effect of treatment [$F(4,34) = 5.02$, $P < 0.01$)]. * Significant difference vs. saline/saline-injected (−/−) controls ($P < 0.05$, Dunnett's test for multiple comparisons). + Significant difference vs. saline/neuropeptide-injected (−/−) animals ($P < 0.01$, Dunnett's test for multiple comparisons).

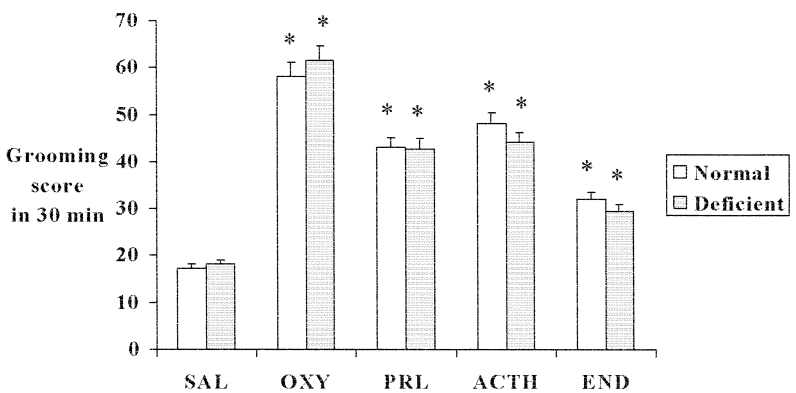

Fig. 4. The expression of excessive grooming induced in dopamine D_2 receptor-deficient mice by i.c.v. injection of neuropeptides made 30 min prior to behavioral testing. Doses of neuropeptides were: 5 ng for oxytocin, 10 ng for prolactin, 10 ng for ACTH-(1-24), and 2 ng for β-endorphin. Values are mean ± S.E.M. Two-way ANOVA revealed a significant effect of treatment [$F(4,34) = 5.21$, $P < 0.01$)]. * Significant difference vs. saline-injected normal (+/+) controls ($P < 0.01$, Dunnett's test for multiple comparisons).

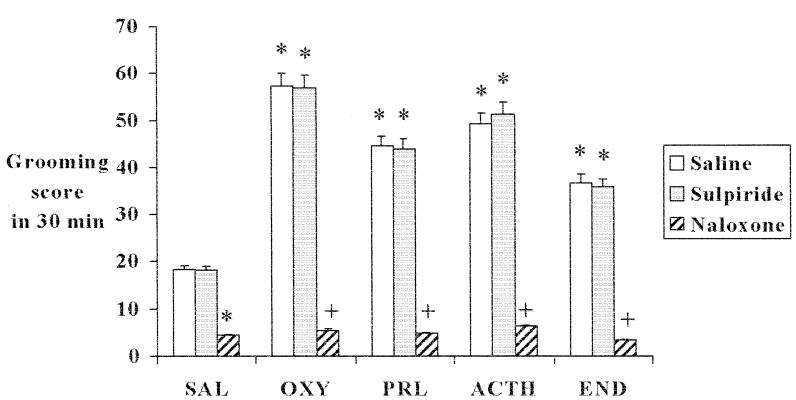

Fig. 5. The effect of sulpiride or naloxone on the expression of excessive grooming induced in dopamine D_2 receptor-deficient mice by i.c.v. injection of neuropeptides. Values are mean ± S.E.M. Two-way ANOVA revealed a significant effect of treatment [$F(4,34) = 5.12$, $P < 0.01$)]. * Significant difference vs. saline/saline-injected (−/−) controls ($P < 0.05$, Dunnett's test for multiple comparisons). + Significant difference vs. saline/neuropeptide-injected (−/−) animals ($P < 0.01$, Dunnett's test for multiple comparisons).

basal level of grooming lower than that of controls also exhibited an increase of novelty-induced grooming but to a level much smaller [significant effect of treatment ($P < 0.01$) and genotype ($P < 0.05$)]. Interestingly, when β-endorphin was injected, both normal and dopamine D_1 receptor-null mice exhibited similarly an increased level of novelty-induced grooming.

The injection of the selective dopamine D_2 receptor antagonist, sulpiride did not affect the behavioral activation induced by any of the neuropeptides [oxytocin, prolactin, ACTH-(1-24) or β-endorphin]. In contrast, the systemic injection of the non-selective opioid receptor antagonist, naloxone was followed by a total suppression of the residual grooming activity in dopamine D_1 receptor-null mice [significant effect of treatment ($P < 0.01$), Fig. 3].

Dopamine D_2 receptor-deficient mice showed a level of excessive grooming induced by neuropeptides [oxytocin, prolactin, ACTH-(1-24) and β-endorphin] similar to that of ($+/+$) normal mice [significant effect of treatment ($P < 0.01$), Fig. 4]. Furthermore, the excessive grooming induced by oxytocin, prolactin, ACTH-(1-24) or β-endorphin was not affected by the peripheral injection of sulpiride or naloxone (Fig. 5).

4. Discussion

The neurotransmitter dopamine is expressed in brain pathways involved in many types of behavior, including spontaneous grooming and stretching-yawning syndrome (Mogilincka and Klimek, 1977; Breese et al., 1987). The relative contributions of different dopamine receptors subtypes in dopamine-mediated behaviors have been difficult to determine because of the poor pharmacological specificity of most currently available dopamine receptors agonists and antagonists. The availability of transgenic knockout mice has recently provided a tool for assessing the role of dopamine receptors in behavior.

Neuropeptide-induced excessive grooming in rodents has long been related to dopamine neurotransmission in the brain. The grooming elicited by small doses of morphine administered peripherally to rats appears to be dependent on intact dopaminergic system (Ayan and Randrup, 1973; Cools et al., 1974). Low doses of the non-selective dopamine receptors antagonists, haloperidol or flufenazine markedly suppress ACTH-induced excessive grooming (Wiegant et al., 1977). In particular, the dopaminergic nigro-striatal and nigro-accumbens systems seem to be involved in the behavioral effect of ACTH (Gispen et al., 1980; Gispen and Isaacson, 1981). Prolactin-induced excessive grooming is also related to dopamine neurotransmission in the brain, as this behavior is suppressed by haloperidol injected peripherally (Drago et al., 1980) or into the striatum or the nucleus accumbens (Drago et al., 1981a, 1984; Drago, 1988). Excessive grooming induced by oxytocin is also blocked by peripheral on intracerebral haloperidol (Drago et al., 1986a,b). Furthermore, substance P-induced grooming depends on the action of this neuropeptide with the A10 dopaminergic brain area (Stinus et al., 1978).

Dopamine D_1 receptor-deficient mice show various behavioral alterations including a suppression of rearing behavior (Drago et al., 1994) that is not stimulated by acute injection of cocaine (Xu et al., 1994a; Drago et al., 1996). The deficit of rearing behavior expression has been considered as a result of dysfunction in motivational aspects of behavior (Drago et al., 1996). Dopamine D_1 receptor-mutant mice evidence unaltered sniffing and sifting responses to the selective dopamine D_1 receptor agonist, A68930 (Clifford et al., 1998). These animals may show either no change in locomotor activity (Drago et al., 1994, 1996) or hyperactivity (Xu et al., 1994b). When cocaine is administered to dopamine D_1 receptor-null mice, either no change in locomotor activity (Miner et al., 1995) or dose-dependent hypoactivity (Xu et al., 1994a) may be observed. Both control and mutant dopamine D_1 receptor-deficient mice exhibit cocaine conditioned place preference (Miner et al., 1995) and behavioral sensitization to amphetamine, as animals pre-exposed and tested with amphetamine were more active than mice acutely tested with the drug. However, the amphetamine-induced locomotor hyperactivity is significantly reduced when dopamine D_1 receptor-deficient mice are compared to similarly treated controls, indicating that the sensitized response is less pronounced in dopamine D_1 receptor-deficient mice (Crawford et al., 1997).

The present results show that novelty-induced grooming is less expressed in dopamine D_1 receptor ($-/-$) mice than in dopamine D_2 receptor ($-/-$) and their littermate controls. A decrease in spontaneous grooming of dopamine D_1 receptor-null mice was already described by Xu et al. (1994b). However, recently Clifford et al. (1998) have reported that dopamine D_1 receptor-deficient mice show unaltered grooming activity, while intense grooming to the highest dose of the selective dopamine D_1 receptor agonist, A68930, was attenuated but still occurred to significant excess compared to vehicle controls. Furthermore, grooming was attenuated (while intense grooming was unaltered) when the 'anomalous' selective dopamine D_1 receptor agonist, SKF83959 was administered. It is difficult to explain the difference of these results compared to the present findings: it may depend on variables in behavioral analysis, different parameters measured, difference in animal strain. Possible differences may also apply to the genetic histories of the subjects and the locations of testing in the two studies. A compensatory mechanism may also have occurred in knockout animals. In fact, the possibility has been hypothesized that a D_1-like receptor other than D_{1A} may mediate typical D_1-like function and participate in D_1/D_2 receptor interactions through an influence of compensatory mechanisms consequent to developmental absence of D_{1A} receptors (Clifford et al., 1998). It is clear

that full acceptance of the singular importance of the D_1 receptors on grooming will depend on resolution of these conflicting results.

The behavioral changes in dopamine D_1 receptor-deficient mice may differ considerably from the behavioral consequences of dopamine D_2 or D_3 receptors elimination. Mice without functional dopamine D_2 receptors show more Parkinsonian-like motor dysfunction with severe akinesia (Baik et al., 1995) and fail to exhibit any opiate rewarding effect (Maldonado et al., 1997). In contrast, dopamine D_3 receptor-deficient mice are hyperactive, with increased locomotor activity and rearing in the open field test (Accili et al., 1996). These animals enter open arms of the plus maze significantly more often and longer than their littermates, but do not differ in closed-arm entries, an index of general activity (Steiner et al., 1997). Furthermore, dopamine D_3 receptor-mutant mice exhibit increased behavioral sensitivity to concurrent stimulation of dopamine D_1 receptors and dopamine D_2 receptors (Xu et al., 1997). Thus, dopamine receptor subtypes contribute to dopamine control of behavior in a qualitatively different manner.

The present study also shows that magnitude of neuropeptide-induced excessive grooming is reduced in dopamine D_1 receptor-deficient mice compared to that of their littermates. In contrast, dopamine D_2 receptor-null mice show a normal level of behavioral activation. Only the i.c.v. injection of β-endorphin is followed by induction of excessive grooming both in $D_1(-/-)$ and $D_2(-/-)$ mice. The participation of opiate receptors in the residual neuropeptide-induced excessive grooming of dopamine D_1 receptor-null mice and in the full expression of this behavior observed after β-endorphin administration is confirmed by the suppression of grooming after peripheral injection of the opiate receptor antagonist, naloxone. In contrast, the injection of the selective dopamine D_2 receptor antagonist, sulpiride, does not affect the behavioral activation in mice. Furthermore, neuropeptide-induced excessive grooming in dopamine D_2 receptor-deficient mice appears also to be suppressed by naloxone. It is known that this drug may suppress excessive grooming induced by different neuropeptides, such as ACTH-(1-24) (Gispen and Wiegant, 1976), prolactin (Drago et al., 1981b; Drago, 1988), and oxytocin (Pedersen et al., 1988). Furthermore, β-endorphin induces excessive grooming (Gispen et al., 1976; Wiegant et al., 1978) that is totally blocked by naloxone (Gispen and Isaacson, 1981). Thus, the present findings suggest that naloxone-sensitive opioid receptors are functionally expressed both in dopamine D_1 receptor- and dopamine D_2 receptor-null mice, and that these receptors may be responsible for the residual grooming activity in dopamine D_1 receptor-deficient mice and the full expression of this behavior in dopamine D_2 receptor-mutant animals observed after central application of neuropeptides.

In conclusion, these data suggest that dopamine D_1 receptors play a pivotal role in the expression of novelty-induced grooming in mice. In contrast, dopamine D_2 receptors seem to be not important for the expression of this behavior. Furthermore, neuropeptide-enhanced grooming involves dopamine D_1 receptors, but not dopamine D_2 receptors. However, neurotransmitters other than dopamine (e.g., endorphins) may play a supplementary role in neuropeptide-enhanced grooming in mice.

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