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Grooming in the Mouse Is Stimulated by the Dopamine D_1 Agonist SKF 38393 and by Low Doses of the D_1 Antagonist SCH 23390, but Is Inhibited by Dopamine D_2 Agonists, D_2 Antagonists and High Doses of SCH 23390

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STARR, B S AND M S STARR *Grooming in the mouse is stimulated by the dopamine D_1 agonist SKF 38393 and by low doses of the D_1 antagonist SCH 23390, but is inhibited by dopamine D_2 agonists, D_2 antagonists and high doses of SCH 23390* PHARMACOL BIOCHEM BEHAV 24(4) 837–839, 1986 —The effects of manipulating dopamine D_1 and D_2 receptors on grooming was studied in the mouse SKF 38393 (D_1 agonist) and low doses of SCH 23390 (D_1 antagonist) promoted grooming activity SCH 23390 in neuroleptic doses, RU 24213 (D_2 agonist), apomorphine and amphetamine (mixed D_1/D_2 agonists) and haloperidol (D_2 antagonist) all suppressed the tendency of normal mice to groom, though probably by different mechanisms Duration and frequency of grooming could be influenced differentially by these drugs The findings suggest opposing roles for dopamine D_1 and D_2 receptors in the expression of grooming in the mouse

Grooming mouse SKF 38393 SCH 23390 RU 24213 Amphetamine Apomorphine Haloperidol

BRAIN dopamine receptors are of two types, called D_1 and D_2 [13]. Since there is a close correlation between the motor effects of centrally-acting dopaminergic drugs and their affinities for the D_2 receptor [10], what behaviours, if any, are attributable to the D_1 site? It was hoped that studies with first-generation selective D_1 agonists, such as SKF 38393 [11], and D_1 antagonists like SCH 23390 [4], would provide a definitive answer to this question, but the findings have proved equivocal

Although SKF 38393 is a powerful motor stimulant in animals with supersensitive dopamine receptors, it has little or no demonstrable dopaminomimetic action in normal animals [13]. One reason for this apparent inefficacy is that the responses mediated by D_1 stimulation, being rather weak, are not superimposable on the high level of motor activity ordinarily exhibited by animals when they are introduced to a new environment. Molloy and Waddington [7,8] showed recently, however, that if baseline activity is reduced to a low level by extensive habituation to the test surroundings, then a variety of locomotor, sniffing, rearing and grooming responses to SKF 38393 treatment can be disclosed. As these experiments recorded the frequency of appearance of a given behaviour, the nature of the responses awaits further clarification.

During the course of a more detailed study of the effects of SKF 38393 on locomotion in the mouse [12], excessive grooming was noticed in naive animals, similar to that reported for habituated rats [7]. Further examination of this behaviour revealed that dopaminergic drugs modified the time spent grooming independently of the prevalence of grooming, and that grooming could be potentiated both by SKF 38393 and SCH 23390 (D_1 agents), whereas D_2 agonists and antagonists had the opposite effect. This report presents these findings and considers the possibility that the two types of dopamine receptors may have opposing roles in the expression of grooming

METHOD

Animals

Male albino mice (Tuck) weighing 35–40 g were housed in groups of ten in temperature-regulated surroundings under a normal light-dark cycle, and allowed free access to food and water.

TABLE 1

EFFECTS OF D_1 AND D_2 DOPAMINERGIC DRUGS ON DURATION AND FREQUENCY OF GROOMING IN THE MOUSE

Drug	Dose (mg/kg)	Grooming response	
		Time (sec)	Episodes
Controls	—	80 1 ± 10 9	6 1 ± 0 6
SKF 38393	1	79 4 ± 12 4	5 0 ± 0 4
	3	130 8 ± 26 9*	5 3 ± 1 7
	10	151 8 ± 22 6*	7 3 ± 1 4
	30	103 1 ± 22 0	8 3 ± 1 9
RU 24213	0 15	31 5 ± 6 1*	2 1 ± 0 2*
	1 5	12 7 ± 1 0*	1 9 ± 0 2*
	5	0*	0*
Amphetamine	0 1	90 7 ± 16 1	5 7 ± 0 2
	0 5	101 5 ± 14 3	9 3 ± 1 8
	2	28 5 ± 13 5*	8 2 ± 2 4
	10	35 6 ± 12 2*	9 7 ± 1 4*
SCH 23390	0 002	193 0 ± 14 5*	11 0 ± 0 5*
	0 01	182 1 ± 16 9*	9 8 ± 0 6*
	0 05	7 0 ± 2 1*	1 0 ± 0 2*
Haloperidol	0 05	79 1 ± 10 7	5 0 ± 1 0
	0 2	58 5 ± 16 7	5 2 ± 1 0
	0 4	56 7 ± 10 8*	3 3 ± 0 3*

Each result is the mean (±SEM) of at least eight determinations
*$p<0.01$ versus controls by Dunnett's test

Drugs

SKF 38393 (Smith, Kline and French), SCH 23390, (Schering), d-amphetamine sulphate (Koch Light), haloperidol (Searle), apomorphine hydrochloride (MacFarlan Smith) and RU 24213 (Roussel) were dissolved in a demineralised water to give an injection volume of 5 ml/kg. The latter two drugs were injected subcutaneously 15 min beforehand, the rest were given intraperitoneally 20 min prior to behavioural testing The dissolution of haloperidol was aided with one drop glacial acetic acid, while apomorphine was protected against oxidation by including 0.2 mg/ml ascorbic acid

Procedure

Mice were injected with drug or vehicle (water), returned to their home cage, then placed singly onto the floor of a rectangular Perspex box (30×25×20 cm high) to which they had previously been exposed for two periods of 8 min each Motor activity was monitored automatically by under-floor proximity sensors (Panlab model 0603) for 8 min, while rearing frequency and the number of episodes and time spent grooming were recorded by direct observation with the aid of hand-held counters Results were compared by analysis of variance and Dunnett's test

RESULTS

Control mice initially moved about the test arena moderately rapidly and displayed a high incidence of rearing, which later gave way to periods of immobility and whole body grooming During the 8 min observation period control animals averaged 6 1±0 6 grooming episodes lasting a total of 80 1±10 9 sec (Table 1), together with 65 8±3 4 rears and 492 2±14 1 sensor activations

The D_1 agonist, SKF 38393, increased the time spent grooming (but not the frequency) at 3 and 10 mg/kg, without affecting rearing or locomotion All elements of the animal's normal grooming repertoire were enhanced and the behaviour did not become stereotyped

RU 24213, a D_2 stimulant, depressed all motor acts monotonically Both the incidence and duration of grooming were decreased (Table 1), while locomotion (e g , 37 1±1 7% controls at 1 5 mg/kg, $p<0.01$) became slow and ponderous with head-down sniffing, and rearing was practically abolished (e g , 4 7±0 5% controls at 1 5 mg/kg, $p<0.01$) Identical results were obtained with apomorphine (not shown)

The effects of amphetamine, an indirectly-acting D_1/D_2 agonist, were quite different No measurable changes in motor activity were detected up to 0 5 mg/kg Rearing was attenuated at 2 mg/kg (12 9±4 4% controls, $p<0.01$) and accentuated at 10 mg/kg (215 8±56 1% controls, $p<0.01$), at which point the mice exhibited discontinuous running and an elevated motor score (166 1±19 4% controls, $p<0.01$) The obvious fragmentation of behaviour at these higher doses was reflected in a greater incidence of grooming, even though the overall time spent in pursuance of this activity was considerably reduced (Table 1)

The D_1 blocking drug, SCH 23390, was next tested with a view to finding a dose that could be used to block SKF 38393 without impairing behaviour *per se* In the event such a drug mixture was not administered as interestingly SCH 23390 itself, at 2 and 10 μg/kg, markedly stimulated both the frequency and duration of grooming throughout the trial period, seemingly at the expense of rearing (38 6±1 7 and 50 1±4 8% controls respectively, $p<0.01$) and locomotion (75 3±5 1 and 68 0±7 2% controls respectively, $p<0.01$), which declined As with SKF 38393, all aspects of grooming were exaggerated No such effects were apparent at 0 5 μg/kg SCH 23390 (not shown), while at 50 μg/kg SCH 23390 the animals became quiescent and consequently reared (13 6±1 2% controls, $p<0.01$), locomoted (31 1±4 7% controls, $p<0.01$) and groomed to a smaller extent ($p<0.01$, Table 1)

Haloperidol, a D_2 antagonist, depressed rearing and grooming monophasically over the range 0 05–0 4 mg/kg, but only at the highest dose was grooming attenuated significantly (Table 1), when rearing and locomotion averaged 22 7±1 6 and 31 9±2 2% controls respectively ($p<0.01$) The state of hypoactivity induced by this drug was indistinguishable from that elicited by SCH 23390

DISCUSSION

Molloy and Waddington [7] noticed that as vehicle-treated rats became accustomed to their surroundings they eventually ceased to groom, yet could be made to do so if administered the R-enantiomer of SKF 38393 The present results show that the racemic mixture of SKF 38393 elicits a similar non-stereotyped form of perseverative grooming in the mouse, and therefore confirms the link between dopamine D_1 receptors and this particular response category Under the experimental conditions we employed however, extensive habituation was not an essential prerequisite for demonstrating a grooming response to SKF 38393, and consequently it was the duration and not the prevalence of grooming that was promoted by this compound (see [7])

In the earlier study [7], the conclusion that SKF 38393-induced grooming is a D_1-mediated phenomenon because it can be blocked by the D_1 antagonist SCH 23390 [4], though probably correct, nevertheless overlooks the fact that habituating baseline motor behaviour to a very low level, in order to facilitate the appearance of grooming with the agonist, also effectively obscures any cataleptogenic action of the antagonist (e.g., [1,3]). This was clearly not the case for our non-habituated mice, which remained highly active, and where as little as 50 μg/kg SCH 23390 severely impeded all motor activity, including grooming. We were concerned, therefore, that the ability of SCH 23390 to suppress the natural tendency of mice to groom, might be attributable indirectly to the inhibition of all voluntary motor acts (albeit by D_1 receptor blockade), and not to a specific effect on grooming itself. It was whilst attempting to find a sub-neuroleptic amount of SCH 23390, with which to verify the D_1 specificity of SKF 38393 in these experiments, that we uncovered instead an exaggerated grooming response with microgram doses of our so-called antagonist. The close resemblance between the repetitive grooming initiated by SKF 38393 and that obtained with SCH 23390, invites speculation that similar mechanisms may underlie both phenomena.

One explanation for these results is that SCH 23390 may, in fact, stimulate D_1 receptors at the very low dose levels employed here. For example, Meller *et al* [6], in their study of D_2 receptor binding, concluded that "... SCH 23390 may therefore have unusual mixed agonist/antagonist properties, resulting in unusual functional effects." As far as we know, however, there is no evidence that SCH 23390 can behave as a partial agonist at the D_1 site, though the hypothesis is clearly an attractive one. Alternatively, SCH 23390 could be functioning as a D_1 antagonist in our experiments and may facilitate grooming non-selectively by suppressing incompatible behaviours, such as rearing and locomotion [5]. Such a proposal is difficult to test directly, but it finds support in the observation that grooming emerges as the dominant behaviour in mice as their locomotor activity declines during the course of within-session habituation, as noted here. That is not to say that immobility *per se* necessarily favours the emergence of grooming, since mice rendered hypoactive with larger doses of SCH 23390, or with the D_2 antagonist haloperidol [1], registered an unchanged or diminished grooming response. Whether the benzazepine and the butyrophenone share a common mechanism is debatable, since low doses of haloperidol spared grooming and high doses could be non-selective. In this connection it is interesting to note that blocking D_2 receptors with the more discriminating D_2 agent, metoclopramide, abolished the stereotypic actions of apomorphine and unmasked excessive grooming in their place [8]. These results support the idea that loss of function of D_2 receptors does not impair grooming, but instead allows this response to be freely expressed via unblocked D_1 receptors.

Since stereotypy and grooming are evidently incompatible behaviours, it follows that the D_2 agonist RU 24213 [2], and the mixed D_1/D_2 agonist apomorphine [10], decrease grooming in a different manner to antagonists, most likely by promoting compulsive head-down sniffing. Similarly with amphetamine, which increases grooming frequency yet paradoxically reduces the overall time spent in pursuance of this activity. It probably achieves this by unselectively increasing the rate of responding of all motor acts, thereby causing the animal's pattern of behaviour to become increasingly fragmented [9] as the result of rapid switching between grooming and other forms of behaviour. In conclusion, therefore, it may well be that the expression of grooming in the mouse is normally governed by the balance of dopamine's activity at its two different receptor sites.

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