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CROSS TOLERANCE OR TACHYPHYLAXIS AMONG VARIOUS PSYCHOTOMIMETIC AGENTS ON CATS

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DOM, 2,5-dimethoxy-4-methylamphetamine, a perception-distorting psychotomimetic agent, has been demonstrated to elicit a marked behavioral syndrome in cats. This syndrome is antagonized by a pretreatment of DOM. This tachyphylaxis has been examined to determine the ability of various other types of psychotomimetic agents to antagonize the DOM-induced syndrome. Mescaline and d-LSD but not l-LSD could prevent the occurrence of the DOM-induced behavior. Ditran, tryptamine and d-amphetamine did not antagonize DOM. Thus it appears that the perception-distorting psychotomimetic agents exhibit either cross tachyphylaxis or cross tolerance and may share a common mechanism of action.

Psychotomimetic cross tachyphylaxis	Cross tolerance	Ditran	Amphetamine
2,5-Dimethoxy-4-methylamphetamine	Mescaline	LSD	Tryptamine

1. Introduction

Data from previous experiments assessing cortical EEG and reticular multiple unit activity have suggested that various psychotomimetic agents can be differentiated into at least two classes, the central nervous system (CNS) stimulants and the perception-distorting psychotomimetics (Wallach and Gershon, 1971; Wallach et al., 1972, 1973). The first group includes such compounds as amphetamine, methamphetamine, cocaine, l-dopa, methylphenidate, and phenmetrazine. The perception-distorting compounds include lysergic acid diethylamide (LSD),2,5-dimethoxy-4-methylamphetamine (DOM), and mescaline. In man the CNS stimulants elicit a paranoid, schizophrenic-like syndrome and the latter agents more characteristically induce perceptual distortions when abused.

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In order to further confirm the similarities of various perception-distorting psychotomimetics, we have attempted to demonstrate cross tolerance or tachyphylaxis between several of the perception-distorting psychotomimetics and DOM. In a previous report (Wallach et al., 1972) we observed that cats receiving a moderately high dose of DOM reliably exhibited a syndrome of grossly abnormal behavior which could be completely antagonized by a 24 hr pretreatment with DOM. This was determined to be tachyphylaxis as larger doses of DOM failed to overcome this antagonism. In the present study, changes in the occurrence of signs comprising this syndrome were evaluated after a standard dose of DOM in cats previously treated with various doses of the test compounds. Use of DOM as a 'standard' for comparison purposes was based on previous data indicating that the various signs in the DOM syndrome encompassed nearly all of those produced by other perception-distorting psychotomimetics (Wallach et al., 1972). The reverse sequence of drug administration was not used.

2. Materials and methods

A colony of mongrel male and female cats weighing 2.0–4.5 kg were used. Between experiments these cats were caged with ad lib access to food and water. For testing the cats were taken to another laboratory, weighed and placed individually into an observation cage. This cage was a wooden box approximately 60 cm on each side with a metal pan and sawdust for a floor and one wall a plexiglass door. Following accomodation to the cage, drugs were administered i.p. and the behavior was observed.

Two 1 hr testing sessions were employed for each animal. In test 1, each animal was treated with a dose of a test compound or a 4 mg/kg dose of DOM (DOM control). Test 2 occurred 24 hr later and consisted of administration of 4 mg/kg DOM to all animals. The occurrence of the following signs were noted every 15 min for 1 hr during both test sessions: forelimb and hindlimb extension, back arching, forelimb crossing, swiping at face and eyes, claw unsheathing, teeth baring, piloerection, salivation and extreme miosis. Signs occurring during the observation periods were counted (maximum of nine signs) for each cat. Each sign was counted once whether the sign was observed one or more times during the hour. Following the observations, the cat was returned to its home cage and not used again for at least 10 days (Wallach and Gershon, 1971, 1972; Wallach et al., 1972).

The drugs used were 2,5-dimethoxy-4-methylamphetamine HCl (DOM), mescaline hemisulfate, d-amphetamine sulfate, tryptamine HCl, ditran HCl, d-LSD-25, and l-LSD-25. All doses are stated as the salts and the drugs were dissolved in saline for administration. Statistical comparisons between groups were made using Mann–Whitney U-tests (Siegel, 1956).

3. Results

Following a single 4 mg/kg dose of DOM, a characteristic series of signs began to appear within 10 min. These signs included extension of both fore and hind limbs, crossing of the forelimbs, arching of the back, swiping at the face and eyes, unsheathing of the claws, and baring of the teeth. Piloerection and salivation were also prominent. Within 30 to 45 min extreme miosis also occurred. Essentially a complete blockade of DOM signs (median = 1.0) was observed after a second DOM injection of 4 mg/kg 24 hr later (table 1).

Table 1
Median number of perception-distorting psychotomimetic-induced signs observed. Test 1 represents the results observed following the pretreatment on the first day. Test 2 represents the observations following 4 mg/kg DOM. A low score on test 2 represents cross tolerance or tachyphylaxis.

Drug	Number	Test 1 score	Test 2 score
DOM			
4.0 mg/kg	6	9.0	1.0
d-LSD			
0.1 mg/kg	6	2.5	3.0
0.2 mg/kg	5	1.0	0.0
l-LSD			
0.1 mg/kg	4	0.5	8.5 **
0.2 mg/kg	4	0.0	6.0 **
0.4 mg/kg	4	0.0	4.0 **
0.8 mg/kg	5	0.0	6.0 **
Mescaline			
30 mg/kg + 24 hr later	6	3.5	
30 mg/kg		1.5 *	4.0 ***
50 mg/kg	6	3.5	2.5
d-Amphetamine			
2.0 mg/kg	5	1.0	5.5 ***
Tryptamine			
10 mg/kg	4	1.5	6.5 **
Ditran			
0.5 mg/kg	7	0.0	7.0 ***

* $p < 0.05$; comparison with previous Mescaline score during test 1, 24 hr prior to this test.
** $p < 0.005$; comparisons with DOM Score during test 2.
*** $p < 0.002$; comparisons with DOM Score during test 2.

Pretreatment of cats with the active form of LSD (d-LSD) in doses of 0.1 or 0.2 mg/kg did not elicit many signs. The signs produced by d-LSD alone included limb extension and crossing, claw unsheathing, and salivation. Miosis was seldom observed. This pretreatment with d-LSD, however, reduced the number of DOM-induced signs 24 hr later to values similar to a second dose of DOM. Virtually complete antagonism of the effects of DOM occurred at a d-LSD dose of 0.2 mg/kg. Conversely, l-LSD failed to elicit be-

havioral changes in doses up to 0.8 mg/kg, and it also failed to significantly antagonize the DOM response pattern.

Pretreatment with mescaline also elicited a mild DOM-like syndrome. It differed from that produced by d-LSD, in that mydriasis and arching of the back were prominent signs, in addition to unsheathing of claws.

A single 24 hr pretreatment with mescaline, 50 mg/kg, significantly reduced the DOM-induced syndrome. Although a trend toward a reduction in the number of DOM signs also occurred after two pretreatments (48 and 24 hr) with 30 mg/kg of mescaline, this reduction was not statistically significant. Tolerance to the effects of mescaline was also observed. A significant reduction in the number of perception-distorting psychotomimetic-induced signs occurred from one 30 mg/kg pretreatment to the second dose (table 1). Signs reduced included arching of the back, claw unsheathing, and mydriasis. Vomiting was also a prominent feature of mescaline injections (4 out of 6 cats) at both doses, but no reduction in frequency of this response was observed after the second 30 mg/kg dose of mescaline.

Pretreatment with d-amphetamine, tryptamine, or ditran failed to significantly alter the DOM-induced syndrome. With respect to d-amphetamine pretreatment, DOM-induced movements of the forelimbs were somewhat reduced, and miosis was delayed in 2 cats. d-Amphetamine treatment produced stereotyped behavior as previously described (Randrup and Munkvad, 1967; Wallach and Gershon, 1971; Ellinwood, 1969), salivation, and mydrasis in 3 out of 5 cats. Tryptamine administration resulted in miosis and piloerection in some cats and tryptamine only reduced swiping at the face after DOM.

Ditran failed to elicit signs similar to those induced by the perception-distorting psychotomimetics. Mydriasis occurred in all cats, and constant crying was observed in several animals. The mydriasis was still evident 24 hr later. The DOM syndrome following ditran was normal except for a reduction in piloerection in some cats and a delay of onset of miosis.

4. Discussion

The observations in this study tend to confirm the initial classification of psychotomimetic agents into at least 2 categories: the CNS stimulants and the perception-distorting agents. The perception-distorting agents used in this study were capable of eliciting some similar signs including arching of the back, extension of the limbs, crossing of the forelimbs, swiping at the face, unsheathing of the claws and baring of the teeth. Some degree of either cross tolerance or tachyphylaxis could be demonstrated among these perception-distorting agents. This was not totally unanticipated as some cross tolerance has been reported previously for some of these agents in different test systems (Appel and Freedman, 1968; Rosenberg et al., 1963; Sparber and Tilson, 1972; Winter, 1971). The interesting points are that the cross tolerance or tachyphylaxis did not occur with a stereotype-inducing dose of amphetamine, or with a dose of ditran capable of eliciting some marked anticholinergic effects. The specificity of the cross tachyphylaxis or tolerance is demonstrated by the failure of l-LSD to antagonize the DOM syndrome while the perception-distorting d-isomer was an active antagonist.

Since DOM, d-LSD and mescaline were all capable of preventing a subsequent DOM-induced syndrome, it might be postulated that they share a common mechanism of action and that this mechanism of action is temporarily altered in such a manner as to prevent a repeated activation. This could be explained by a prolonged antagonism at the receptor or by a disruption of a neurohumoral mechanism. In our previous study of DOM, it appeared that the mechanism of action was serotoninergic and postsynaptic inasmuch as the usual presynaptic manipulations of adrenergic and serotoninergic systems did not alter the DOM-induced response and marked changes in serotonin levels of the diencephalon occurred between the two doses (Wallach et al., 1972).

Although we have previously mentioned that mescaline could not elicit a DOM-like response, we observed that some cats, following moderately high doses of mescaline, exhibited some of the characteristic DOM-like signs. These signs, however, were not as dramatic as those following DOM. It should also be pointed out that tolerance to the effects of mescaline alone was observed only among signs comprising the DOM syndrome and did not occur to emesis.

It thus appears that there is a similarity in the mechanisms of action between various perception-

distorting psychotomimetic agents. The cross tachyphylaxis or tolerance observed may become a useful tool for identifying their mechanisms of action.

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