THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS
Vol. 182, No. 1

Printed in U.S.A.

2,5-DIMETHOXY-4-METHYLAMPHETAMINE (DOM), A NEUROPHARMACOLOGICAL EXAMINATION[1]

MARSHALL B. WALLACH, EITAN FRIEDMAN AND SAMUEL GERSHON

Neuropsychopharmacology Research Unit, Department of Psychiatry, New York University Medical Center, 550 First Avenue, New York, New York

Accepted for publication April 7, 1972

ABSTRACT

WALLACH, MARSHALL B., EITAN FRIEDMAN AND SAMUEL GERSHON: 2,5-Dimethoxy-4-methylamphetamine (DOM), a neuropharmacological examination. J. Pharmacol. Exp. Ther. **182:** 145–154, 1972.

The neuropharmacology of 2,5-dimethoxy-4-methylamphetamine (DOM) was examined. A single 8 mg/kg dose of DOM elicits electroencephalogram hypersynchrony and elevates reticular formation multiple unit activity. A second dose, 24 hours later, is without effect. The behavioral effects of a single dose of DOM are antagonized by methysergide, brom-lysergic acid diethylamide (brom-LSD), chlorpromazine and tripelennamine, but not by reserpine, α-methyl-*p*-tyrosine, *p*-chlorophenylalanine, phenoxybenzamine, propranolol, atropine and diphenhydramine. Cyproheptadine was weakly antagonistic. Methysergide and brom-LSD induced intermittent hypersynchrony in the electroencephalogram and prevented the continuous hypersynchrony induced by DOM. DOM caused an increase in medullary norepinephrine and a slight increase of serotonin in the diencephalon and cerebral hemispheres. A second dose of DOM again increased the medullary norepinephrine but reduced diencephalic serotonin. DOM induces hypersynchrony and behavioral changes similar to those induced by perception distorting psychotomimetic drugs such as LSD and mescaline. It does not induce the electroencephalogram desynchronization or stereotyped behavior previously described for amphetamine. DOM appears to act on postsynaptic serotonin receptors.

The psychotomimetic drug, 2,5-dimethoxy-4-methylamphetamine (DOM), has been reported to be approximately 100 times more potent as a hallucinogen than mescaline and 1/30 as potent as lysergic acid diethylamide (LSD) in man (Snyder *et al.*, 1967). Shulgin *et al.* (1969) have determined that DOM is 80 times as strong as mescaline in inducing psychotomimetic effects. In man this agent can produce visual hallucinations of a kaleidoscopic nature as well as distortions of image (Snyder *et al.*, 1967; Hollister *et al.*, 1969; Faillace *et al.*, 1970).

There is insufficient data describing the effects of DOM in animals. Low doses of DOM produce alerting of the rabbit electroencephalogram (EEG) by acting at the level of the medulla (Fugimori and Himwich, 1968). At higher doses DOM produces catatonia and convulsions (Florio *et al.*, 1969). In the rat, DOM elicits some excitation followed by catatonia, convulsions and

Received for publication October 18, 1971.
[1] This work was supported by U.S. Public Health Service Grant MH 12383.

Send reprint requests to: Dr. Marshall B. Wallach, Department of Psychiatry, Room HN 419, New York University Medical Center, 550 First Ave., New York, N.Y. 10016.

death. Disruptions in the conditioned behavior of cats occur after 0.25 mg/kg of DOM i.p. Higher doses produce abnormal "attitudes with opened mouth," protruding tongue, hunting-type behavior (Florio *et al.*, 1969), staring, pawing motions in the air and aggressive behavior consisting of growling, hissing, biting and clawing (Idänpään-Heikkilä *et al.*, 1969).

Current studies were undertaken to determine the effects of DOM on the cat. In particular, it was of interest to compare the effects of DOM to those observed after various other types of psychotomimetic agents previously examined. The perception distorting psychotomimetic agents, such as LSD, mescaline and phencyclidine, elicit a hypersynchronous or intermittently hypersynchronous EEG in the cat associated with inappropriate behavior (Winters *et al.*, 1969). Amphetamine, cocaine and *l*-dopa, which induce paranoid psychoses in man, produce stereotyped behavior in the cat associated with a desynchronized EEG (Wallach and Gershon, 1971).

Methods

Gross behavioral studies. Cats of either sex weighing between 2.0 and 4.0 kg were placed in a cage approximately 60 × 60 × 60 cm having a Plexiglas door on one side. After the cat's adjustment to the laboratory conditions, the drug or drugs were administered and observations of the cat's behavior were made by a trained observer.

For the antagonism studies, an eight-point rating system was devised to evaluate the degree of antagonism and the ability of the various agents to block part of the syndrome selectively. The parameters utilized were: arching of the back, extension of the limbs, unsheathing the claws, baring the teeth, hissing, abnormal behavior (either crossing of the forelimbs or pawing the face and eyes), extreme miosis and piloerection. Each of these characteristics were observed in over half the cats after 8 mg/kg of DOM. A sign was scored as either being present or absent during the one-hour observation period. When the score indicated a significant reduction of total sympatomatology by a chi square test, a chi square 2 × 2 contingency test was performed on the individual sign scores to determine what modification in the syndrome had occurred.

The following drugs were utilized in an attempt to antagonize the DOM-induced behavioral changes: reserpine (Serpasil), 1 mg/kg; α-methyl-*p*-tyrosine methyl ester HCl, 100 mg/kg twice; atropine sulfate, 2 mg/kg; phenoxybenzamine (Dibenzaline), 3 mg/kg; propranolol, 10 mg/kg; tripelennamine HCl (Pyribenzamine), 6 mg/kg; diphenhydramine (Benadryl), 4 mg/kg; 2-brom-D-lysergic acid diethylamide (BOL-148), 0.5 mg/kg; methysergide, 1 to 2 mg/kg; cyproheptadine, 0.2 to 4.0 mg/kg; *p*-chlorophenylalanine, 100 mg/kg four times in 0.25% methylcellulose; haloperidol (Haldol), 0.2 mg/kg; and chlorpromazine HCl (Thorazine), 4 to 8 mg/kg.

All potential inhibitors were administered i.p. 20 minutes prior to the DOM except α-methyl-*p*-tyrosine methyl ester HCl (20 and 4 hours), *p*-chlorophenylalanine (96, 72, 48 and 24 hours) and reserpine (20 hours) s.c. Agonistic effects of the potential antagonists were minimal but included some miosis and/or piloerection after such agents as α-methyl-*p*-tyrosine, reserpine, propranolol, phenoxybenzamine and cyproheptadine. The DOM potentiated these agonistic actions when they did occur.

Electroneuropharmacology. Adult cats of either sex weight 2 to 3.5 kg were implanted with chronic bipolar subcortical and monopolar cortical electrodes under pentobarbital anesthesia. The stereotaxic placement of the electrode in the reticular formation was at A3, L3 and H(-1), (Jasper and Ajmone-Marsan, 1953). Cortical electrodes were placed over the medial suprasylvian gyrus, the lateral gyrus (visual cortex), the anterior suprasylvian gyrus and the ectosylvian gyrus. The electrodes were soldered to a socket and fixed in dental cement. Stereotaxic placements have been verified histologically in five of the cats; the remaining cats are still alive.

After recovery from surgery, the cats were placed in an environmental chamber (Lehigh Valley Electronics model no. 1440) equipped with a mirror on the back wall and a one-way glass window on the door. Shielded cables from the connector on the cat's head were passed through the top of the chamber to a connector box. The EEG and cervical neck muscle tone were recorded on a Grass (model no. 7) polygraph. The reticular formation multiple unit activity was amplified by two Tektronix FM 122 preamplifiers connected in tandem. The resultant signal was passed through a filter and into a Tektronix 502A oscilloscope. The output from the cathode follower of the oscilloscope was rectified and integrated before being recorded on a Brush Mark 260 recorder. The amplified EEG and the rectified and intergrated electromyogram (EMG) also were recorded on the Brush recorder. This allowed intermittent recording of the EEG at normal speeds and, in parallel, a continuous recording of the reticular formation multiple unit activity, EEG and EMG. Drug-induced changes of all three parameters over a prolonged period of time were visualized readily.

Changes in the multiple unit activity level reflect overall changes in the unit activity of the area being sampled. This technique is especially applicable to pharmacological studies involving the central nervous system and utilizing peripheral drug administration. Utilizing all 3 parameters, changes in the sleep patterns also can be observed and quantitated.

The reticular unit activity levels were recorded on chart paper, measured and calculated in a manner described by Wallach *et al.* (1969). The basal reticular unit activity level was arbitrarily designated as 100% during the rhombencephalic phase of sleep (paradoxical sleep) and all subsequent values were calculated accordingly.

Neurochemistry. The cats were treated with DOM, 8 mg/kg, at 1 or 24 or 1 and 24 hours before sacrifice. All experiments were conducted at the same time of day to minimize the effects of circadian changes in biogenic amine levels. Fifteen minutes prior to sacrifice, 35 mg/kg of pentobarbital (Nembutal) were administered to all the animals. After decapitation, the brains were removed rapidly, rinsed with cold saline and placed on an ice-cooled glass plate. Dissections were performed within 10 minutes after decapitation. The brains were dissected into three regions: cerebral hemispheres, medulla including the medulla oblongata and pons, and diencephalon including the hypothalamus, thalamus, striatum and midbrain. Brain regions were weighed, homogenized in ice-cold 0.4 N perchloric acid containing 0.1% disodium ethylenediamine tetraacetate and centrifuged at 12,000 × *g* for 20 minutes at 4°C. The mean weights (± S.E.) of the dissected brain areas were: cerebral hemispheres, 16.51 ± 0.36 g; medulla, 2.17 ± 0.06 g; and diencephalon, 3.36 ± 0.13 g.

The method used to separate norepinephrine (NE), dopamine (DA) and 5-hydroxytryptamine (5-HT) was a modification of the technique previously described by Neff *et al.* (1971). Potassium perchlorate was precipated by adding 0.9 ml of 10 N potassium acetate to 14.1 ml of the clear supernatant. After centrifugation, the amines in the resultant supernatant were adsorbed on a Dowex 50W-X4, Na^+ form column. The resin was washed with 14 ml of 0.1 M sodium acetate buffer, pH 6, and 5 ml of 0.4 N hydrochloric acid. NE was eluted with 10 ml of 0.4 N hydrochloric acid. DA was eluted with 4 ml of 4 N hydrochloric acid. After washing the column with 3 ml of distilled water, 5-HT was eluted with 4 ml of 0.5 M tribasic sodium phosphate. NE and DA were purified further by alumina adsorption and estimated fluorimetrically by the methods of Anton and Sayre (1962) and Laverty and Taylor (1968), respectively. The 5-HT eluate was extracted into butanol and re-extracted into a phosphate buffer in the presence of heptane. The buffer extract was reacted with ninhydrin according to the method of Snyder *et al.* (1965). Fluorescence was estimated with an Aminco-Bowman spectrophotofluorometer. The recoveries of NE, DA and 5-HT added together to homogenates were 73%, 78% and 93%, respectively.

TABLE 1

Behavioral scores indicating tachyphylaxis induced by DOM

Previous DOM Dose	Time	Current DOM Dose	*N*	Mean Score ± S.E.[a]
mg/kg	*hr*	*mg/kg*		
		2	11	5.00 ± 0.36
		4	5	5.60 ± 0.68
		8	13	6.54 ± 0.88
2	24	2	5	0.80 ± 0.20[b]
2	24	8	6	1.50 ± 0.22[b]
4	24	4	5	1.20 ± 0.49[b]
8	24	8	4	1.00 ± 0.00[b]
8	48	8	4	2.25 ± 0.75[b]
8	96	8	5	4.40 ± 0.24[c]

[a] See "Methods" for details.
[b] $P < .001$ from initial score.
[c] $P < .01$ from initial score.

Results

Gross behavior. Cats administered a single i.p. injection of DOM, 1 or 2 mg/kg, exhibited some abnormal behaviors such as biting in the air, hissing, baring of teeth, unsheathing of claws, withdrawing into a corner of the cage and arching of the back. The signs were often short lasting. This was succeeded within one hour by an abnormal posture characterized by standing or sitting with the head hanging to the floor of the cage and turned sideways. The forelimbs were often crossed and the eyes closed (table 1).

DOM, 4 to 8 mg/kg, consistently induced a more dramatic alteration in behavior. Within five minutes, behavioral abnormalities appeared. These included a marked arching of the back with the forelimbs and hindlimbs placed together, occasional crossing of the forelimbs and swiping at its face and eyes. Hissing, growling, biting at both the air and objects in the cage, baring of the teeth, unsheathing the claws, tremor, tonic limb extension, ataxia, piloerection and extreme miosis also were observed (table 1). If the cage door was opened, some cats would leap with well coordinated movements from the cage to the floor in an attempt to escape.

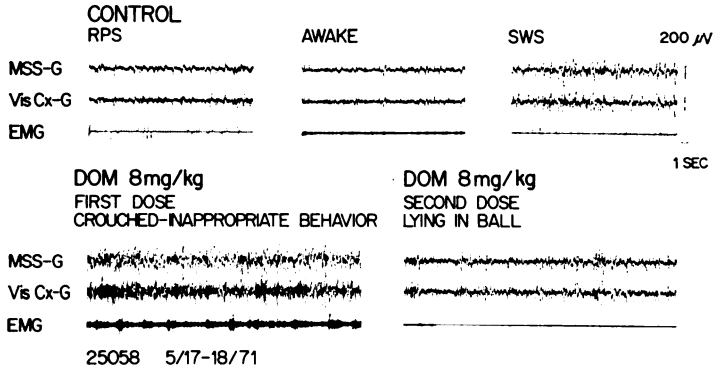

FIG. 1. EEG before and after two doses of DOM 24 hours apart. Note the hypersynchrony after the first dose and the lack of hypersynchrony after the second dose. Abbreviations are: RPS, rhombencephalic phase of sleep (paradoxical sleep); SWS, slow wave sleep; MSS, medial suprasylvian gyrus; Vis Cx, visual cortex; G, ground; EMG, cervical muscle tone.

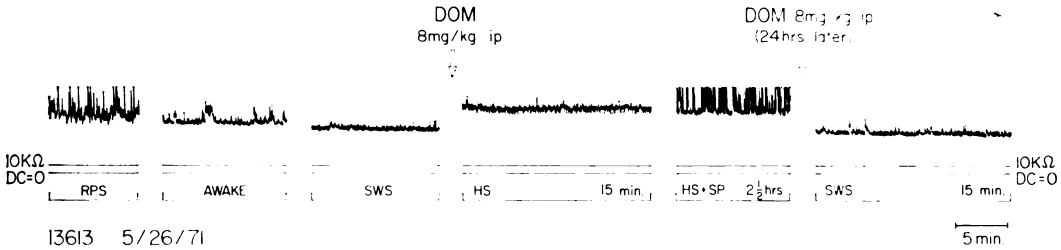

FIG. 2. Reticular formation multiple unit activity before and after two doses of DOM 24 hours apart. Note the difference between the first and second doses. Record reads from left to right. DC = 0 represents no input to the system; 10KΩ represents the noise level with a 10 kilohm resistor substituted for the electrode. Abbreviations are: RPS, rhombencephalic phase of sleep (paradoxical sleep); SWS, slow wave sleep, HS, hypersynchrony; SP, spiking.

Electroneuropharmacological observations. DOM, 2 mg/kg, produced an intermittently hypersynchronous EEG associated with an elevated reticular formation multiple unit activity from a control awake level of 81 to 91% to 98 to 119%. This intermittently hypersynchronous EEG lasted for about one to two hours before becoming mixed with other slow wave and desynchronized frequencies. After 8 mg/kg of DOM, the EEG became continuously hypersynchronous and some spiking or convulsive electrical discharges were observed; however, no behavioral manifestations of seizure activity and no postictal depression were noted (fig. 1). Initially, the reticular formation multiple unit activity was elevated from a control awake level of 77 to 88% to 96 to 117% (fig. 2). During the spiking, a further increase in the unit activity level occurred. The hypersynchronous EEG continued and disintegrated over approximately 12 hours into a generalized slow wave pattern similar to that observed during slow wave sleep. The unit activity levels returned to the control range between 6 and 12 hours after the administration of the first dose of DOM. The first episode of paradoxical sleep usually occurred about 15 hours after the administration of DOM.

Tachyphylaxis to DOM. The administration of a second dose of DOM 24 hours later did not result in the typical DOM syndrome observed after the first dose. The cat curled up and slept. The behavioral rating score after the first administration of 8 mg/kg of DOM was 6.54. After the second administration, 24 hours later, the score was only 1.0 due to a lingering miosis from the first dose. Administration of two doses of DOM, 2 mg/kg, 24 hours apart, resulted in scores of 5.00 and 0.80. If 8 mg/kg of DOM were given after an initial dose of 2 mg/kg, the score was 1.50. The tachyphylaxis gradually remitted over a period of approximately one week (table 1).

After the second dose of DOM, the EEG was dominated by slow waves similar to those seen during slow wave sleep (fig. 1). Occasionally,

some brief periods of what may be intermittent hypersynchrony occurred, especially after a small first and large second dose of DOM. The reticular formation multiple unit activity was reduced markedly from the previous day and was in the range of normal control slow wave sleep; however, there was a slight reduction in the base-line level and fluctuation of the unit activity. Reticular formation unit activity levels after a single administration of DOM, 8 mg/kg, to five cats averaged 96 to 117% and after the second administration of DOM, 8 mg/kg, were 65 to 73%. This was in the range of control slow wave sleep (63–78%). In two cats receiving 2 mg/kg of DOM, the mean unit activity levels were 94 to 112% after the first dose and 64 to 73% after the second dose. In two cats receiving 2 mg/kg of DOM followed at 24 hours by 8 mg/kg the comparable figures were 102 to 126% and 84 to 96%. Paradoxical sleep following the second dose of 8 mg/kg of DOM occurred at about four hours. Thus, the EEG, reticular formation multiple unit activity and gross behavior indicate that there was a marked tachyphylaxis to a second administration of DOM.

Biochemical results. Several changes in the biogenic amine levels occurred after DOM, 8 mg/kg. After a single administration, an increase in the level of NE in the medulla was the only significant ($P < .01$) change detected (fig. 3). However, there was a trend toward an increase in the 5-HT levels in the cerebral hemispheres and the diencephalon (fig. 4). Twenty-four hours after a single dose of DOM, no significant changes from control levels were observed. After a second dose of 8 mg/kg of DOM, the only change from control values detected was the increase in the medullary NE. There was also a significant decrease in the level of 5-HT in the diencephalon after the second dose of DOM as compared with one hour after single administration. No significant changes were observed in DA levels (fig. 5).

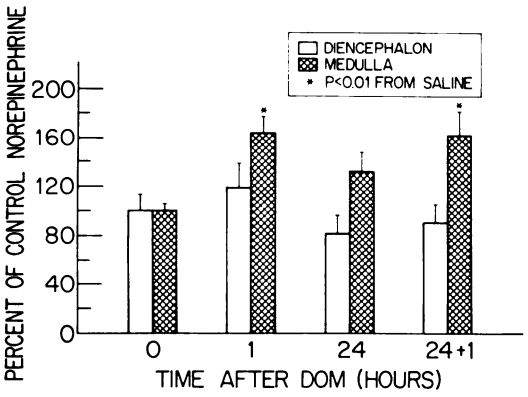

FIG. 3. Effect of 8 mg/kg of DOM on brain NE levels. Control levels were 0.47 ± 0.06 μg/g in the diencephalon and 0.32 ± 0.02 μg/g in the medulla.

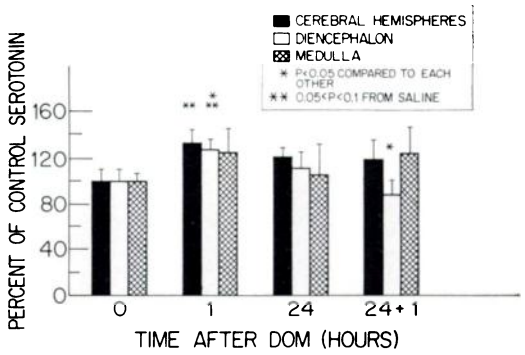

FIG. 4. Effect of 8 mg/kg of DOM on brain 5-HT (serotonin) levels. Control levels were 0.26 ± 0.03 μg/g in the cerebral hemispheres, 0.32 ± 0.03 μg/g in the diencephalon and 0.24 ± 0.02 μg/g in the medulla.

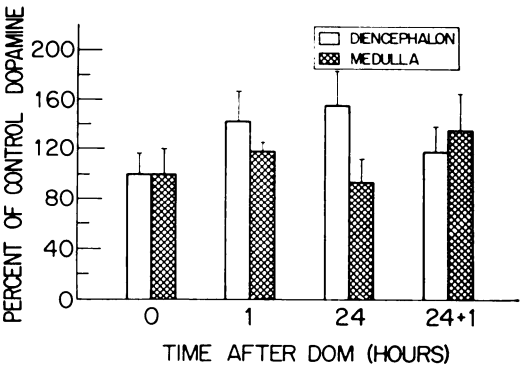

FIG. 5. Effect of 8 mg/kg of DOM on brain DA levels. Control levels were 0.50 ± 0.08 μg/g in the diencephalon and 0.21 ± 0.04 μg/g in the medulla.

Antagonism of DOM effects by various drugs. The effectiveness of various agents in antagonizing the DOM syndrome is summarized in table 2. DOM, 8 mg/kg, when administered without pretreatment, elicited a score of 6.54 ± 0.88 symptoms. Significant reductions in the overall DOM scores were observed after pretreatments with 2-brom-*d*-LSD (BOL-148), methysergide, cyproheptadine, chlorpromazine and tripelennamine.

BOL reduced most of the signs to some extent and increased the latency of onset of the DOM

TABLE 2

Antagonism of the DOM syndrome

Pretreatment	Dose	Time	DOM Dose	*N*	Score ± S.E.	P
	mg/kg		*mg/kg*			
None				13	6.54 ± 0.88	
BOL	0.5	20 min	8	5	4.00 ± 2.35	< .001
Methysergide	1.0	20 min	8	5	3.33 ± 0.33	< .001
	2.0	20 min	8	5	1.80 ± 0.37	< .001
	2.0	20 min	16	5	2.00 ± 0.55	< .001
Cyproheptadine	0.2	20 min	8	5	4.60 ± 0.60	< .01
	0.4	20 min	8	3	6.00 ± 1.15	N.S.
	4.0	20 min	8	5	5.60 ± 0.68	N.S.
Chlorpromazine	4.0	20 min	8	6	4.60 ± 0.60	< .001
	8.0	20 min	8	4	2.75 ± 0.50	< .001
Tripelennamine	6.0	20 min	8	6	4.50 ± 1.76	< .01
Atropine	2.0	20 min	8	5	5.20 ± 1.10	N.S.
Reserpine	1.0	20 hr	8	5	5.20 ± 2.39	N.S.
α-Methyl-*p*-tyrosine	100	20 hr				
	100	3 hr	8	3	6.67 ± 1.53	N.S.
Haloperidol	0.2	20 min	8	3	6.67 ± 0.58	N.S.
Phenoxybenzamine	3.0	20 min	8	3	6.67 ± 0.58	N.S.
Propranolol	10.0	20 min	8	5	6.00 ± 1.00	N.S.
Diphenhydramine	4.0	20 min	8	3	7.00 ± 1.00	N.S.
p-Chlorophenylalanine	100	96 hr				
	100	72 hr				
	100	48 hr				
	100	24 hr	8	3	6.67 ± 1.53	N.S.

syndrome. Methysergide, 2 mg/kg, significantly reduced all the signs except piloerection, limb extension and unsheathing of the claws. The occurrence of these signs was reduced, but not to a significant level.

Cyproheptadine, 0.2 mg/kg, pretreatment significantly decreased the behavioral score following DOM; however, higher doses of cyproheptadine (0.4 and 4.0 mg/kg) were not effective. The lowest dose of cyproheptadine abolished hissing. Slight reductions in the occurrence of baring of the teeth and abnormal behavior were also noted.

Tripelennamine reduced the incidence of teeth baring and abnormal behavior; however, diphenhydramine was not effective in antagonizing the syndrome. Atropine pretreatment induced mydriasis which antagonized the DOM induced miosis.

Chlorpromazine, 8 mg/kg, lowered the scores of most of the symptoms except piloerection, limb extension and unsheathing the claws. Chlorpromazine, 4 mg/kg, reduced the total score, but hissing was the only parameter significantly lowered.

Reserpine and α-methyl-*p*-tyrosine, haloperi-

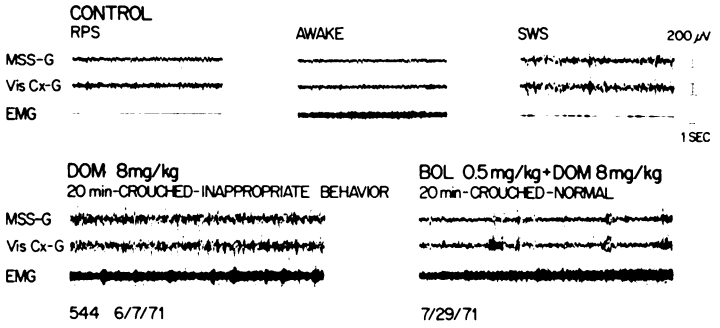

FIG. 6. Antagonism of DOM induced hypersynchrony by BOL. Drug records from two experiments at the same gains and in the same cat. See figure 1 for abbreviations.

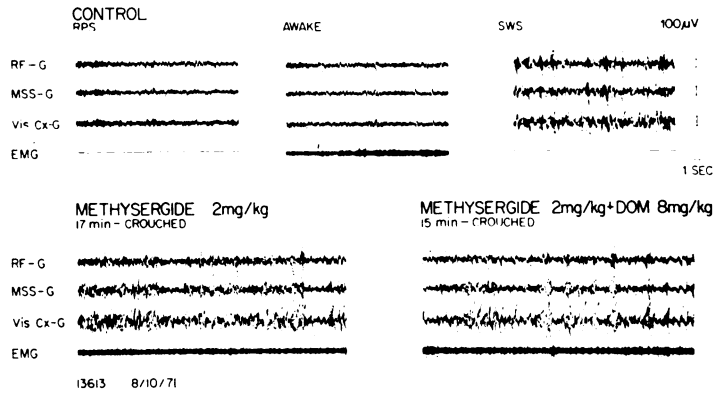

FIG. 7. Effect of methysergide on EEG and DOM induced hypersynchrony. RF, reticular formation; other abbreviations as in figure 1.

dol, phenoxybenzamine, propranolol and *p*-chlorophenylalanine failed to alter the DOM syndrome significantly.

Antagonism of the electroneuropharmacological effects of DOM. Antagonism of the hypersynchrony and elevated reticular formation multiple unit activity by BOL and methysergide were attempted. Both BOL and methysergide elicited some intermittent hypersynchrony before the DOM was administered. The DOM-induced continuous hypersynchrony was delayed after BOL (fig. 6) and only intermittent hypersynchrony was observed with methysergide pretreatment (fig. 7). Two cats received DOM, 8 mg/kg, with and without methysergide, 2 mg/kg, pretreatment. The reticular formation multiple unit activity level was 109 to 123% without the pretreatment and 90 to 105% with the methysergide pretreatment.

Discussion

The gross behavior observed after DOM administration is in agreement with previous descriptions of this syndrome in cats, (Florio *et al.*, 1969; Idänpään-Heikkilä *et al.*, 1969). This behavior is also similar to the response of the cat to large doses of LSD (Elder and Dille, 1962) with the exception that LSD induces mydriasis while DOM causes miosis. The DOM syndrome contrasts markedly with the stereotyped behavior induced by amphetamine (Randrup and Munkvad, 1967; Wallach and Gershon, 1971, 1972).

Winters *et al.* (1969) and Winters and Wallach (1970) postulated that all psychotomimetic agents, when administered to cats, produce a continuum of EEG changes. Initially a desynchronized EEG is followed by intermittent hypersynchrony, then by continuous hypersynchrony. Various states of spiking, with or without electrical silence, and convulsive seizures also are induced by some psychotomimetics. Compounds which produce hallucinations in man are capable of producing at least part of this continuum. DOM, in the dose range exam-

ined, elicited intermittent and continuous hypersynchrony as well as spiking.

This amphetamine derivative, however, did not induce a desynchronized EEG or stereotyped behavior of the nature described for amphetamine (Wallach and Gershon, 1971). This agrees with a modification of the original Winters hypothesis suggesting that there are at least two types of psychotomimetics (Wallach and Gershon, 1971). One group, including such agents as LSD, mescaline and phencyclidine, elicits perceptual distortions in man and hypersynchrony in the cat EEG. The agents eliciting a paranoid psychosis in man are exemplified by amphetamine, cocaine and *l*-dopa. They produce a desynchronized EEG associated with stereotyped behavior in cats. DOM appears to belong to the first group, the perceptual distorting psychotomimetics. In man, DOM elicits visual hallucinations of the kaleidoscopic type and distortions of image (Snyder *et al.* 1967). In cats, DOM elicits a hypersynchronous EEG.

The tachyphylaxis to DOM observed in both behavioral and electrical parameters is more pronounced than the tolerance of the cat to amphetamine (M. B. Wallach, unpublished observations). Mescaline in doses as high as 150 mg/kg does not produce the behavioral syndrome; however, the hypersynchrony does occur. Repeated administration of mescaline at 50 to 100 mg/kg does not produce a rapid induction of tolerance (M. B. Wallach, unpublished observations). Tolerance has been observed in man after administration of increasing doses of DOM over eight days (Hollister *et al.*, 1969).

One possible explanation for the tachyphylaxis after DOM is that DOM is agonistic whereas a metabolite is antagonistic at the same receptor. Under such a situation, the initial dose could elicit its effects and prevent a subsequent response as long as the antagonistic metabolite remains. Idänpään-Heikkilä *et al.* (1969) have demonstrated that after the injection of tritiated DOM, the cat brain tritium disappears in two phases. The rapid decrease in the first hour is succeeded by a very slow disappearance of the remaining radioactivity. During the second phase, the proportion of metabolites of DOM is increasing rapidly, but the total radioactivity remains almost constant between one and six hrs. Thus, it is conceivable that a metabolite of DOM is antagonizing the action of a subsequent dose of DOM.

The tachyphylaxis to DOM cannot be explained by a depletion of catecholamines or 5-HT. The levels of 5-HT are slightly elevated in the cerebral hemispheres and diencephalon after a single dose of DOM, although this change falls short of significance. The trend toward increased 5-HT after the first dose and decreased 5-HT levels in the diencephalon after the second administration of DOM suggests the participation of 5-HT in the syndrome. E. Friedman (unpublished studies) has examined the conversion of labeled tryptophan to labeled 5-HT in hypothalamic slices of cats pretreated with DOM. After the first administration of DOM, the conversion of tryptophan to 5-HT is increased whereas after the second dose it is similar to control values. Increased 5-HT levels have also been observed in rat brain after DOM (Freedman *et al.*, 1970) and LSD (Freedman and Giarman, 1962).

The failure of reserpine, α-methyl-*p*-tyrosine, phenoxybenzamine and propranolol to alter the DOM syndrome argue against a significant contribution of adrenergic mechanisms to the DOM syndrome. All of these agents are capable of entering the mammalian brain (Masuoka and Hansson, 1967; Masuoka *et al.*, 1967).

The ability of methysergide to block the DOM-induced syndrome and the ability of BOL to antagonize it partially and to delay its onset are suggestive of a serotonergic mechanism. Previously, chlorpromazine has been reported to have antiserotonin activity (Schmid *et al.*, 1959; Marrazzi, 1962). The failure of cyproheptadine at high doses to antagonize the DOM-induced syndrome is difficult to explain. Cyproheptadine has been shown to have central activity in this dosage in the cat (Chakrabarty *et al.*, 1967). The lack of effectiveness of diphenhydramine while tripelennamine demonstrated antagonistic activity suggests that tripelennamine may have antiserotonin activity. Antiserotonin activities of tripelennamine have been reported (Meier *et al.*, 1957; Mariani and Villani, 1959; Schmid *et al.*, 1959). Since *p*-chlorophenylalanine did not alter the DOM syndrome, it is presumed that DOM elicits its primary effect directly on a postsynaptic receptor.

If the DOM is acting on the postsynaptic 5-HT receptor, as might be suggested by the failure of *p*-chlorophenylalanine to influence the syndrome, then it becomes difficult to explain the changes in 5-HT metabolism. One possible

explanation is that the changes in 5-HT are secondary to postsynaptic receptor activity. This would imply a feedback system altering 5-HT synthesis or release depending on postsynaptic receptor occupation. Such evidence has not been reported yet.

The induction of intermittent hypersynchrony by both BOL and methysergide precluded a complete answer to their abilities to antagonize the DOM-induced hypersynchrony. If the hypersynchrony is a model for identifying perception-distorting hallucinogens, then BOL and methysergide both should be psychotomimetic. Psychoses or hallucinations have not been reported in man after BOL; however, one report studying BOL in very high dosage for carcinoid syndrome indicated that BOL induced psychic changes like subhallucinogenic LSD doses (Schneckloth *et al.*, 1957). Psychoses after methysergide in man (Hale and Reed, 1962) and a worsening of symptomatology in schizophrenics receiving methysergide (Mendels, 1967; Fish *et al.*, 1969) tend to support the contention that methysergide may be psychotomimetic.

Acknowledgments. The authors thank Dr. A. A. Renzi of The Dow Chemical Company (Midland, Mich.) for supplies of DOM, Miss N. Starr and Mrs. D. Forde for their skillful technical assistance.

References

ANTON, A. H. AND SAYRE, D. F.: A study of the factors affecting the aluminum oxide–trihydroxyindole procedure for the analysis of catecholamines. J. Pharmacol. Exp. Ther. **138:** 360–375, 1962.

CHAKRABARTY, A. S., PILLAI, R. V., ANAND, B. K. AND SINGH, B.: Effect of cyproheptadine on the electrical activity of the hypothalamic feeding centers. Brain Res. **6:** 561–569, 1967.

ELDER, J. T., JR., AND DILLE, J. M.: An experimental study of the participation of the sympathetic nervous system in the lysergic acid diethylamine (LSD) reaction in cats. J. Pharmacol. Exp. Ther. **136:** 162–168, 1962.

FAILLACE, L. A., SNYDER, S. H. AND WEINGARTNER, H.: 2,5-Dimethoxy-4-methylamphetamine: Clinical evaluation of a new hallucinogenic drug. J. Nerv. Ment. Dis. **150:** 119–126, 1970.

FISH, B., CAMPBELL, M., SHAPIRO, T. AND FLOYD, A., JR.: Schizophrenic children treated with methysergide (Sansert). Dis. Nerv. Syst. **30:** 534–540, 1969.

FLOIRO, V., LIPPARINI, F., SCOTTI DE CAROLIS, A. AND LONGO, V. G.: EEG and behavioral effects of 2,5-methoxy-4-methylamphetamine (DOM, STP). Arch. Int. Pharmacodyn. Thér. **180:** 81–99, 1969.

FREEDMAN, D. X. AND GIARMAN, N. J.: LSD-25 and the status and level of brain serotonin. Ann. N.Y. Acad. Sci. **96:** 98–107, 1962.

FREEDMAN, D. X., GOTTLIEB, R. AND LOVELL, R. A.: Psychotomimetic drugs and brain 5-hydroxytryptamine metabolism. Biochem. Pharmacol. **19:** 1181–1188, 1970.

FUGIMORI, M. AND HIMWICH, H. E.: Electroencephalographic alerting sites of *d*-amphetamine and 2,5-dimethoxy-4-methylamphetamine. Nature (London) **220:** 491–494, 1968.

HALE, A. R. AND REED, A. F.: Prophylaxis of frequent vascular headache with methysergide. Amer. J. Med. Sci. **243:** 92–98, 1962.

HOLLISTER, L. E., MACNICOL, M. F. AND GILLESPIE, H. K.: An hallucinogenic amphetamine analog (DOM) in man. Psychopharmacologia **14:** 62–73, 1969.

IDÄNPÄÄN-HEIKKILÄ, J. E., MCISAAC, W. M., HO, B. T., FRITCHIE, G. E. AND TANSEY, L. W.: Relation of pharmacological and behavioral effects of a hallucinogenic amphetamine to distribution in cat brain. Science (Washington) **164:** 1085–1087, 1969.

JASPER, H. H. AND AJMONE-MARSAN, C.: A Stereotaxic Atlas of the Diencephalon of the Cat, National Research Council of Canada, Toronto, 1953.

LAVERTY, R. AND TAYLOR, K. M.: The fluorometric assay of catecholamines and related compounds: Improvements and extensions to the hydroxyindole technique. Anal. Biochem. **22:** 269–279, 1968.

MARIANI, L. AND VILLANI, R.: Selectivity of antagonistic effects toward histamine or serotonin of some phenothiazine derivatives and of some classical antihistaminics. Boll. Soc. Ital. Biol. Sper. **35:** 1598–1602, 1959.

MARRAZZI, A. S.: Synaptic and behavioral correlates of psychotherapy and related drug actions. Ann. N. Y. Acad. Sci. **96:** 211–226, 1962.

MASUOKA, D., APPELGREN, L. E. AND HANSSON, E.: Autoradiographic distribution studies of adrenergic blocking agents. I. ^{14}C phenoxybenzamine (Bensylyt NFN) an α-receptor-type blocking agent. Acta Pharmacol. Toxicol. **25:** 113–122, 1967.

MASUOKA, D. AND HANSSON, E.: Autoradiographic distribution studies of adrenergic blocking agents. II. ^{14}C propranolol, β-receptor-type blocker. Acta Pharmacol. Toxicol. **25:** 447–455, 1967.

MEIER, R., TRIPOD, J. AND WIRZ, E.: Classification d'une série d'antagonistes de la sérotonine et analyse de ses points d'attaque vasculaires périphériques. Arch. Int. Pharmacodyn Thér. **109:** 55–77, 1957.

MENDELS, J.: The effect of methysergide (an antiserotonin agent) on schizophrenia: A preliminary report. Amer. J. Psychiat. **124:** 849–852, 1967.

NEFF, N. H., SPANO, P. F., GROPPETTI, A., WANG, C. T. AND COSTA, E.: A simple procedure for evaluating the synthesis rate of norepinephrine, dopamine and serotonin in rat brain. J. Pharmacol. Exp. Ther. **176:** 701–710, 1971.

RANDRUP, A. AND MUNKVAD, I.: Stereotyped activities produced by amphetamine in several animal species and man. Psychopharmacologia **11:** 300–310, 1967.

SCHMID, E., ZICHA, L., SCHEIFFARTH, F. AND BÜTTNER, O.: Untersuchungen über den antagonismus von antihistaminen gegen serotonin. Arzneimittel-Forschung **9:** 474–476, 1959.

SCHNECKLOTH, R., PAGE, I. H., DEL GRECO, F. AND CORCORAN, A. C.: Effects of serotonin antago-

nists in normal subjects and patients with carcinoid tumors. Circulation **16:** 523–532, 1957.

SHULGIN, A. T., SARGENT, T. AND NARANJO, C.: Structure-activity relationships of one-ring psychotomimetics. Nature (London) **221:** 537–541, 1969.

SNYDER, S. H., AXELROD, J. AND ZWEIG, M.: A sensitive and specific fluorescence assay for tissue serotonin. Biochem. Pharmacol. **14:** 831–835, 1965.

SNYDER, S. H., FAILLACE, L. AND HOLLISTER, L.: 2,5-dimethoxy-4-methylamphetamine (STP): A new hallucinogenic drug. Science (Washington) **158:** 669–670, 1967.

WALLACH, M. B. AND GERSHON, S.: A neuropsychopharmacological comparison of *d*-amphetamine, *l*-dopa and cocaine. Neuropharmacology **10:** 743–752, 1971.

WALLACH, M. B. AND GERSHON, S.: The induction and antagonism of central nervous system stimulant-induced stereotyped behavior in the cat. Eur. J. Pharmacol. **18:** 22–26, 1972.

WALLACH, M. B., WINTERS, W. D., MANDELL, A. J. AND SPOONER, C. E.: A correlation of EEG, reticular multiple unit activity, and gross behavior following various antidepressant agents in the cat IV: Electroencephalogr. Clin. Neurophysiol. **27:** 563–573, 1969.

WINTERS, W. D., MORI, K., WALLACH, M. B., MARCUS, R. J. AND SPOONER, C. E.: Reticular multiple unit activity during a progression of states induced by CNS excitants III: Electroencephalogr. Clin. Neurophysiol. **27:** 514–522, 1969.

WINTERS, W. D. AND WALLACH, M. B.: Drug induced states of CNS excitation: A theory of hallucinosis. *In:* Psychotomimetic Drugs, ed. by D. H. Efron, pp. 193–214, Raven Press, New York, 1970.