Int. J. Neuropharmacol., 1964, 2, 273–277. Pergamon Press. Printed in Gt. Britain. [4 tables, 13 refs.]

ANTIMESCALINE PROPERTIES OF SOME LYSERGIC ACID DERIVATIVES*

J. BORSY, Zs. HUSZTI and M. FEKETE
Research Institute for Pharmaceutical Industry, Budapest, Hungary

INTRODUCTION

MESCALINE, one of the oldest hallucinogens, was isolated and chemically identified by SPÄTH (1919). Mescaline or 3,4,5-trimethoxyphenyl-ethylamid is closely related to the sympathomimetic amines. This chemical similarity, besides the recently gained knowledge about catecholamine metabolism, renewed the interest in the effects and metabolism of mescaline. The papers of BLASCHKO (1959), AXELROD (1958b), and of others (AXELROD *et al.* 1958a; AXELROD and TOMCHICK, 1958) made it evident that the catecholamines, adrenaline, noradrenaline and dopamine, are *o*-methylated in intermediary metabolism.

DEEGAN and COOK (1958), CHEN and BOHNER (1960), and ourselves (BORSY *et al.*, 1961) have reported on the antagonism between several tranquilizing agents and mescaline. A well known effect of mescaline in the mouse is the scratch-reflex stereotypy which is measurable by means of a suitable registering device. Another type of reaction to mescaline, notably enhanced orientational motor activity has been described (BORSY *et al.*, 1961).

As CHEN and BOHNER (1960) stated, the mescaline-stereotypy easily can be antagonised by lysergic-acid diethylamide (LSD). In view of this, we questioned whether various derivatives of lysergic acid, among them some hallucinogens, also influence the stereotypy and central excitation by mescaline in mice.

METHODS

The mescaline-stereotypy was registered with a counter-connected oscillometer equipped with a different capsule. The animals received subcutaneous injections of 60 mg/kg mescaline and were placed on a rubber membrane 8 cm in diameter. After the orientational reflex wore off 25 min after drug injection, the number of scratching episodes was counted during the following 10 min.

The compounds were also tested as antagonists of mescaline-induced hypermotility during orientation reflex. The drugs were injected intraperitoneally to groups of five mice. An equal number of animals receiving physiological saline solution was used as control. Thirty min later, 100 mg/kg of mescaline were given subcutaneously to all the animals. After another 30 min they were placed in an activity cage where the amount of their activity was recorded for half-an-hour.

The central antiserotonin effect was measured according to TEDESCHI and co-workers (1959). Rats treated with 50 mg/kg iproniazid given by mouth were given lysergic acid derivatives subcutaneously. Thirty min later, they received an intravenous injection

* Presented at the Second International Pharmacological Meeting, Prague, 20–23 August, 1963.

of 70 mg/kg of DL-5-hydroxytryptophan (5-HTP). After 15 min, the animals were put into the activity measuring cage, and the intensity of the tremors was measured during the following 15 min.

The peripheral antiserotonin effect was tested in butabarbital-narcotised rats. Paw oedema was produced by the injection of 5 μg/kg serotonin. After treatment with the drugs, the decrease in inflammation was measured volumetrically and compared to that of untreated controls.

RESULTS

The antagonism of mescaline action by D-lysergic acid diethylamide (LSD), 2-bromo-LSD (BOL-148), 1-methyl-D-lysergic acid butanol-amide (Methysergyl, Deseryl) and dihydroergotamine (DHE), respectively, was studied in 160 mice. The hallucinogenic LSD proved to be the most active antagonist of mescaline with an ED_{50} of 31 μg/kg. BOL-148 was slightly less potent, with an ED_{50} of 80 μg/kg. DHE, with an ED_{50} of 84 μg/kg, was almost as potent. The weakest inhibitor was Methysergyl which had an ED_{50} greater than 500 μg/kg (Table 1).

TABLE 1. THE INHIBITORY EFFECT OF LYSERGIC ACID DERIVATIVES UPON THE STEREOTYPE SCRATCH-REFLEX DUE TO MESCALINE IN MICE

Number of animals	Compounds	Dose in μg/kg i.p.	Total activity SR	Inhibition in %	approx. ED_{50} μg/kg	PR LSD-25=1·0
22	0·9%NaCl + M	0·1 ml/10g	$2024 \pm ^{156.2}$	—		
11	M + LSD-25	25·0	$1172 \pm ^{184.9}$	42·7		
12	M + LSD-25	50·0	$704 \pm ^{98.5}$	65·5		
11	M + LSD-25	100·0	$409 \pm ^{53.7}$	80·0	31·0	1·0
16	0·9%NaCl + M	0·1 ml/10g	$1833 \pm ^{247.0}$	—		
14	M + BOL-148	50·0	$1132 \pm ^{120.4}$	38·3		
10	M + BOL-148	100·0	$935 \pm ^{130.6}$	49·0		
10	M + BOL-148	200·0	$370 \pm ^{48.4}$	79·9	80·0	0·39
10	0·9%NaCl + M	0·1 ml/10g	$1771 \pm ^{225.5}$	—		
14	M + Methysergyl	500·0	$953 \pm ^{110.7}$	45·2	>500·0	>0·06
10	0·9%NaCl + M	0·1 ml/10g	$1713 \pm ^{248.1}$	—		
12	M + DHE	50·0	$1045 \pm ^{126.8}$	39·2		
8	M + DHE	100·0	$827 \pm ^{107.6}$	51·7	84·0	0·37

M = standard of mescaline-SO_4 = 60mg/kg s.c.
SR = Scratching reflex. PR = Potency ratio
The drugs were injected simultaneously
10 min total activity was determined 25 min after injection of the drugs.

It is evident from Table 2 that LSD (25–50 μg/kg) completely abolished mescaline hypermotility. A similar inhibition was also elicited by BOL-148 but the dose required was much greater (200 μg/kg). DHE (200 μg/kg) and Methysergyl (500 μg/kg) were not active.

We then investigated the possible relationship between the antimescaline and central and peripheral antiserotonin effects of lysergic acid derivatives.

Table 3 shows the effect of lysergic acid derivatives on 5-HTP-induced tremor. LSD had a very strong inhibitor action; the tremor was inhibited to 60 per cent by a dose of 1 mg/kg, and to 75·2 per cent by 3 mg/kg. BOL-148 was effective only at a much greater dose, while DHE and Methysergyl were not active.

TABLE 2. THE INHIBITORY EFFECT OF LYSERGIC ACID DERIVATIVES UPON MESCALINE-INDUCED HYPERMOTILITY IN MICE

Number of groups	Compounds	Dose in μg/kg i.p.	30 min total activity $\pm S_x$	Change in %
15	0·9%NaCl + 0·9%NaCl	2 × 0·1 ml/10g	$155 \pm ^{10.7}$	—
17	0·9%NaCl + M	0·1 ml/10g	$318 \pm ^{16.4}$	+ 106
8	LSD-25 + M	25·0	$129 \pm ^{6.6}$	— 17
8	LSD-25 + M	50·0	$126 \pm ^{11.6}$	— 19
14	0·9%NaCl + 0·9%NaCl	2 × 0·1 ml/10g	$181 \pm ^{10.3}$	—
13	0·9%NaCl + M	0·1 ml/10g	$326 \pm ^{14.4}$	+ 80
8	BOL-148 + M	200·0	$189 \pm ^{15.8}$	+ 5
7	0·9%NaCl + 0·9%NaCl	2 × 0·1 ml/10g	$216 \pm ^{13.7}$	—
7	0·9%NaCl + M	0·1 ml/10g	$386 \pm ^{38.9}$	+ 79
7	Methysergyl + M	500·0	$377 \pm ^{51.4}$	+ 15
8	0·9%NaCl + 0·9%NaCl	2 × 0·1 ml/10g	$168 \pm ^{13.1}$	—
6	0·9%NaCl + M	0·1 ml/10g	$315 \pm ^{23.4}$	+ 88
7	DHE + M	200·0	$303 \pm ^{12.7}$	+ 80

M = standard dose of mescaline-SO_4-100·0 mg/kg s.c.

TABLE 3. POTENCY OF LYSERGIC ACID DERIVATIVES IN ANTAGONIZING 5HTP [70mg/kg. i.v.] -INDUCED TREMOR IN RATS PRETREATED WITH IPRONIAZID [50MG/KG PER OS=1]

Number of animals	Compounds	Dose in mg/kg s.c.	15 min total activity $\pm S_x$	Change in %
27	0·9%NaCl		$6400 \pm ^{824}$	—
10	LSD-25	3·0	$1582 \pm ^{236}$	—75·2
12	LSD-25	1·0	$2537 \pm ^{421}$	—60·0
8	LSD-25	0·3	$6304 \pm ^{974}$	— 1·4
14	BOL-148	3·0	$2628 \pm ^{541}$	—58·9
8	BOL-148	1·0	$8145 \pm ^{733}$	— 4·2
8	Methysergyl (UML-491)	3·0	$5279 \pm ^{802}$	— 1·7
8	DHE	3·0	$7057 \pm ^{908}$	+11·0

In agreement with Cerletti's data (FANCHAMPS *et al.*, 1960), BOL-148 was more active than LSD in reducing paw oedema. However, the strongest antiserotonin effect was that shown by Methysergyl; a dose of 0·1 mg/kg was sufficient to reduce serotonin-oedema by 68·3 per cent during the first hour and by 73·1 per cent during the second hour. This effect was four times greater than that of LSD. DHE, even at the high dose of 400 μg/kg, had no antiserotonin effect (Table 4).

TABLE 4. THE INHIBITORY EFFECT OF LYSERGIC ACID DERIVATIVES AGAINST SEROTONIN-INDUCED PAW OEDEMA IN RATS ANAESTHESIZED WITH BUTABARBITAL [100 MG/KG I.P.]

Number of animals	Compounds	Dose in mg/kg s.c.	Percentage inhibition of oedema 1h	2h
12	0·9%NaCl + S	2·0 ml	—	—
8	LSD-25 + S	0·2	35·0	12·2
6	LSD-25 + S	0·4	66·5	62·8
12	0·9%NaCl + S	2·0 ml	—	—
10	BOL-148 + S	0·2	44·0	38·5
16	0·9%NaCl + S	2·0 ml	—	—
8	Methysergyl + S [UML-491]	0·1	68·3	73·1
8	0·9%NaCl + S	2·0 ml	—	—
8	DHE + S	0·4	4·5	10·0

S = standard dose of serotonin creatine sulphate = 5 μg/paw
The compounds were injected subcutaneously 30 min after serotonin treatment

DISCUSSION

In hallucinogenic LSD inhibits both stereotypy and hypermotility elicited by mescaline. DHE and Methysergyl, which are not hallucinogenic, also antagonize stereotypy but do not affect hypermotility. BOL-148 is the least active, but it is more effective in suppressing stereotypy than hypermotility. Thus, the hallucinogenic and non-hallucinogenic lysergic acid derivatives can be distinguished by their effects against the scratch-relax and hypermotility elicited by mescaline. It seems possible that these two mescaline actions have different mechanisms; measuring the antagonism of hypermotility appears to be the more reliable procedure used for testing antimescaline activity.

Our results indicate the existence of a connexion between the central antiserotonin and mescaline antagonizing effects of the lysergic acid derivatives. Both LSD and BOL-148 inhibit the tremor elicited by the combined injection of iproniazid and 5-HTP; DHE and Methysergyl are completely inactive. However, Methysergyl considerably reduces the oedema elicited by serotonin, and at the same time, has no appreciable antimescaline effect.

FRIEDHOFF and GOLDSTEIN (1962) have shown that intermediates in the metabolism of mescaline have more profound behavioural and pharmacologic effects than does mescaline itself. We therefore tested whether the metabolism of mescaline by hepatic mitochondria (prepared after BURKARD *et al.*, 1962) was altered by the above lysergic acid derivatives in concentrations of $2{\cdot}8\text{–}5\times10^{-4}$ M/l. These compounds did not change the metabolism of mescaline *in vitro*. Thus, an inhibition of mescaline metabolism cannot explain the antimescaline activity of LSD.

In this series of compounds, a strong peripheral antiserotonin potency is not associated with either psychotomimetic or antimescaline properties, as was shown with Methysergyl. It is probable that both LSD and mescaline act on the same receptors; low concentrations of LSD having an inhibitory effect on mescaline without causing a direct effect. This is not impossible for, according to DHAWAN and GUPTA (1961), LSD given in low doses does not affect the spontaneous activity of the animals, although when given at this dose it does inhibit certain central structures, such as the emetic center.

Zusammenfassung—Wir haben die Wirkung des Lysergsäurediäthylamids (LSD-25), 2-Bromlysergsäurediäthylamids (BOL-148), des Methysergyls (UML-491) und des Dihydroergotamins (DHE) auf den durch Mescalin hervorgerufenen "scratch reflex" und auf die Hypermotilität in der Maus untersucht. Die erstere Wirkung wurde mit einem oszillometrischen Zähler, die letztere mit der Dews'schen Photozellen-Methode registriert. Wir fanden, dass hinsichtlich der Hemmung der Mescalin-"scratch episodes" das LSD-25 am meisten wirkungsvoll war, indem es in einer Dosis von 25 μg/kg, i.p., eine 42·7%-ige und in einer von 50 μg/kg eine 65·5%-ige Hemmung herbeibrachte. BOL-148, bzw. DHE waren weniger aktiv und Methysergyl am wenigsten.

Die durch Mescalin (100 mg/kg, s.c.) hervorgerufene zentrale Hypermotilität wurde in gruppenweise angelegten Tieren durch diselben Dosen des LSD-25 aufgehoben. Eine gleich starke Hemmung wurde mit 200 μg/kg BOL-148, i.p. erreicht, während Methysergyl und Dihydroergotamin in derselben Dosis ohne Wirkung blieben. In weiteren Untersuchungen haben wir die Substanzen auf periphere und zentrale Antiserotonin-Aktivität geprüft. Die periphere Aktivität wurde von der Hemmung des mit Serotonin erzeugten Pfotenödems an mit Butabarbital (100 mg/kg, i.p.) narkotisierten Ratten beurteilt. Unter den geprüften Substanzen zeigte das Methysergyl die stärkste Hemmwirkung, LSD-25 und BOL-148 waren in dieser Hinsicht viel schwächer. DHE war auch in einer Dosis von 400 μg/kg wirkungslos.

Auf zentralen Antiserotonin-Effekt wurden die Substanzen an mit Iproniazid und 5-Hydroxytryptophan vorbehandelten Ratten untersucht. Allein LSD-25 und BOL-148, die beide über eine starke Antimescalin-Wirkung verfügen, waren imstande, den in der obigen Art erzeugten Tremor zu hemmen.

REFERENCES

AXELROD, J., INSCOE, J. K., SENOH, S., and WITKOP, B. (1958a). *o*-Methylation, the principal pathway for the metabolism of epinephrine and norepinephrine in the rat. *Biochim. biophys. acta* **27:** 210–211.

AXELROD, J., SENOH, S. and WITKOP, B. (1958b). *o*-Methylation of catecholamines *in vivo*. *J. biol. Chem.* **233:** 697–701.

AXELROD, J. and TOMCHICK, R. (1958). Enzymatic *o*-methylation of epinephrine and other catechols. *J. biol. Chem.* **233:** 702–705.

BLASCHKO, H. (1959). The development of current concepts of catecholamine formation. *Pharmacol. Rev.* **11:** 307–316.

BORSY, J., FEKETE, M. and CSIZMADIA, Zs. (1961). Antimescaline effect of trioxazine [N-(3,4,5-trimethoxybenzoyl)-tetrahydro-1,4-oxazine]. *Acta Physiol. Acad. Sci. Hung.* **19:** 27–32.

BURKARD, W. P., GEY, K. F. and PLETSCHER, A. (1962). Differentiation of monoamine oxidase and diamine oxidase. *Biochem. Pharm.* **11:** 177–182.

CHEN, G. and BOHNER, B. (1960). A study of certain CNS depressants. *Arch. int. Pharmacodyn.* **125:** 1–20.

DEEGAN, J. F. and COOK, L. (1958). A study of the anti-mescaline property of a series of CNS active agents in mice. *J. Pharmacol.* **122:** 17A.

DHAWAN, B. N. and GUPTA, G. P. (1961). Antiemetic activity of D-lysergic acid diethylamide. *J. Pharmacol.* **133:** 137–139.

FANCHAMPS, A., DOEPFNER, W., WEIDMANN, H. and CERLETTI, A. (1960). Pharmakologische Charakterisierung von Deseril einem Serotonin-Antagonisten. *Schweiz. Med. Wochenschrift.* **90:** 1040–1046.

FRIEDHOFF, A. T. and GOLDSTEIN, M. (1962). New developments in metabolism of mescaline and related amines. *Ann. N.Y. Acad. Sci.* **96:** 1–13.

SPÄTH, E. (1919). Uber die Anhalonium-alkaloide. *Mh. Chem.* **40:** 129–154.

TEDESCHI, D. H., TEDESCHI, R. E. and FELLOWS, E. J. (1959). The effects of tryptamine on the central nervous system, including a pharmacological procedure for the evaluation of iproniazid-like drugs. *J. Pharmacol.* **126:** 223–232.