

LSD 540

Psychotropic drugs. Ed. by S. Garattini,
V. Ghetti.
Elsevier, Amsterdam, London, New York,
Princeton 1957, p. 460.

THE COMPARISON OF THE PSYCHOTIC EFFECT OF TRYPTAMINE DERIVATIVES WITH THE EFFECTS OF Mescaline AND LSD-25 IN SELF-EXPERIMENTS

S. SZÁRA

Central State Institute for Nervous and Mental Diseases, Budapest (Hungary);
Forschungsabteilung, Psychiatrische und Nervenlinik der Freien Universität, Berlin (Germany)

INTRODUCTION

Indolealkylamines have been considered for a long time as a group of active substances of rather slight pharmacological and almost no psychiatric interest. Renewed attention has been focused on them since the discovery of the presence of 5-hydroxytryptamine in blood, in the enterochromaffin cell system, spleen, kidney, and the central and peripheral nervous tissue. An excellent review on the pharmacology of indolealkylamines by ERSPAMER appeared in 1954, and many other reviews have appeared on 5-hydroxytryptamine or serotonin (AMIN *et al.*¹; FREYBERGER *et al.*¹¹; GADDUM *et al.*¹²; HIMWICH¹³; LANGEMANN¹⁷; PAGE²⁰; ROTHLIN). The tryptamine derivatives have been of interest only in connection with their effect on blood pressure. Data on their effect on the central nervous system can be found only sporadically (NIEUWENHUIZEN¹⁸; SPEETER AND ANTHONY²⁴). Our attention towards their possible psychotic action was attracted by the works of FISH, JOHNSON, AND HORNING⁹ on *Piptadenia* alkaloids among which they found bufotenine, N,N-dimethyltryptamine, and their N-oxides. In experiments on animal they found these drugs to have psychotic effects, but experiments on humans were made only with bufotenin by FABING. We therefore decided to make self-experiments and experiments on normal volunteers with N,N-dimethyltryptamine and with the N,N-diethyl compound also (Fig. 1).

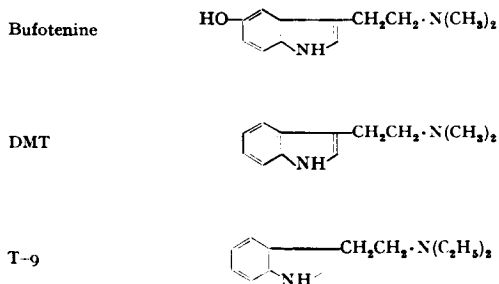


Fig. 1. The chemical constitution
of bufotenine, DMT and T-9.

METHODS AND MATERIALS

The *N,N*-dimethyltryptamine (DMT) and the *N,N*-diethyltryptamine (T-9) were obtained synthetically by the method of SPEETER AND ANTHONY.

For the purpose of purification the amines were distilled in high vacuum. For the experiments, sterile aqueous solutions of the hydrochloric salts were prepared and used in a concentration of 30 mg per ml. The lethal doses estimated in white mice by the usual method were 135 mg/kg in the case of DMT, and 120 mg/kg in the case of T-9.

Although the substances have been not very toxic in mice, we were very cautious in the self-experiments.

In the peroral experiments, starting from $\frac{1}{4}$ mg and increasing the dose up to 150 mg no observable psychic or vegetative effects were found. After the unsuccessful peroral experiments, intramuscular experiments were made. In this titration series other physicians of the Institute of Budapest took part. The doses administered were 10 mg, increasing to 150 mg (*i.e.* 2 mg/kg body weight). Psychotic effects were observed from 30 mg, *i.e.* 0.2 mg/kg body weight; they reached their optimum in doses about 0.7–1.0 mg/kg body weight. On further increasing the doses the psychotic symptoms were suppressed by the vegetative and organic symptoms. Therefore the further experiments on normal volunteers were made with the above-mentioned optimal dose. A detailed paper on the results obtained with normal volunteers, is to appear in *Psychiatria et Neurologica* (SAI-HALÁSZ *et al.*²³).

THE SELF-EXPERIMENTS

The purpose of this report is to compare the psychotic effect of tryptamine derivatives with the well-known effect of mescaline and lysergic acid diethylamide in self-experiments. I believe that this method of experimentation is one of the best ways of obtaining direct information on subtle psychopathological phenomena, which are of great importance in understanding the schizophrenic syndrome.

TABLE I
THE DATA OF SELF-EXPERIMENTS

Substance	Dose	Admin.	Date	Place
I. Mescaline	0.35 g	per os	Dec. 1955	Budapest
II. LSD-25	100 μ g	per os	Dec. 1956	Vienna
III. DMT	0.25 mg–150 mg	per os	March–April 1956	Budapest
DMT	75 mg	i.m.	April 1956	Budapest
DMT	75 mg	i.m.	June 1956	Debrecen
DMT	60 mg	i.m.	March 1957	Berlin
IV. T-9	60 mg	i.m.	Nov. 1956	Budapest

The experiments were carried out over a period of 16 months. I took mescaline at Christmas-time 1955, and the LSD-25 was tested in Vienna at the Psychiatric Clinic of the University, by courtesy of Prof. Dr. HOFF and Docent Dr. ARNOLD, in December 1956. The first intramuscular administration of DMT occurred at the end of April 1956, and was followed by the experiments on normal volunteers. We reported

References p. 466.

the results at the Annual Meeting of the Hungarian Physiological Society in Debrecen. During this meeting I made the second intramuscular experiment in order to get an electroencephalographic recording. A third DMT-experiment and some biochemical investigations were made in Berlin at the Research Department of the Psychiatric and Neurologic Clinic of the Free University, by the courtesy of Prof. Dr. SELBACH. The T-9-experiment was made intramuscularly in November 1956 in Budapest.

I shall not go into details about the effects of mescaline and LSD-25 because I am not able to add any new aspects to that well-known picture. Nevertheless, the chief features of these experiments will be mentioned later. At present I shall only describe in more detail the symptoms of DMT and T-9 model psychoses, in view of the lack of such reports in the literature up to now.

(a) *The DMT-experiments*

As mentioned above, DMT ingested *per os* has no observable effect. But an intramuscular injection of 30 mg could already produce some mydriasis and subjectively some perception disturbances. The larger the dose, the more striking are the symptoms. About the self-experiment made with 1.0 mg/kg, *i.e.* 75 mg DMT in total, I can report the following:

In the third or fourth minute after the injection vegetative symptoms appeared, such as tingling sensation, trembling, slight nausea, mydriasis, elevation of the blood pressure and increase of the pulse rate. At the same time eidetic phenomena, optical illusions, pseudo-hallucinations, and later real hallucinations, appeared. The hallucinations consisted of moving, brilliantly coloured oriental motifs, and later I saw wonderful scenes altering very rapidly. The faces of the people seemed to be masks. My emotional state was elevated sometimes up to euphoria. At the highest point I had compulsive athetoid movements in my left hand. My consciousness was completely filled by hallucinations, and my attention was firmly bound to them; therefore I could not give an account of the events happening around me. After $\frac{3}{4}$ -1 hour the symptoms disappeared, and I was able to describe what had happened.

In the second intramuscular DMT-experiment, the duration in time and the symptoms were mainly the same.

At the third DMT-experiment, the dose was somewhat smaller (60 mg); the symptoms were thus milder, but qualitatively the same.

(b) *The T-9-experiment*

The symptoms of the T-9-experiment are briefly as follows. About 15 minutes after the injection of 60 mg of T-9 came the same vegetative symptoms as described for DMT. The illusions, hallucinations, and the athetoid compulsive movements in the left hand were the same as for DMT. But the alteration of the surrounding world and the emotional reaction to them were strong and impressive. The mask-like faces of the persons, the dream-like mysteriousness of the objects and the room gave me the feeling that I had arrived in another world, entirely different and queer and full of secrecy and mystery. This wonderful but strange world attracted me at one moment, but the next moment I did not want to accept it. I became perplexed; I did not know what I ought to do. I began to walk anxiously up and down, and said: "I ought to do something, I must!" There was a peculiar double orientation in space

and time: I knew where I was, but I was inclined to accept this strange world as a reality, too. The dusk of the room was lightened for some minutes, and again the light was switched off, and that seemed to me as if this period might be an entire epoch, filled with events and happenings, but at same time I knew that only several minutes had passed.

(c) *The comparison of the results*

I should like to compare the effects of the two tryptamine derivatives outlined above with the effect of mescaline and LSD-25. The most outstanding differences can be established in their time of duration.

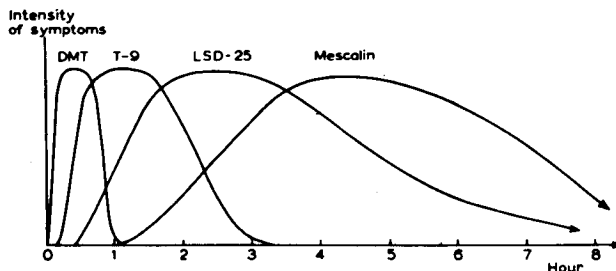


Fig. 2. Schematic course of the self-experiments.

In Fig. 2 it can be seen that the duration of the DMT-induced model psychosis is about one hour, that of T-9 is about three hours, while the LSD- and mescaline symptoms lasted for 8–10 hours. The onset of the symptoms in the case of tryptamine derivatives is essentially quicker than the onset of the others. The elevation of the dose of DMT did not produce a longer state of intoxication, but the symptoms were more organic. It is remarkable that in all the four model psychoses the symptoms developed and passed away in wave form.

The special symptoms are demonstrated in Table II.

TABLE II
THE MAIN SYMPTOMS OBSERVED IN SELF-EXPERIMENTS

Symptoms	Mescaline	LSD-25	DMT	T-9
1. Vegetative symptoms	—	—	Coincided with the other symptoms	
2. Athetoid movements	—	—	+	—
3. Illusions	++	++	+++	+++
4. Hallucinations	—	—	++	+
5. Disturbances of				
a. spatial perception	+++	+++	+++	+++
b. time perception	+	+	+	+++
6. Bodily sensations	+	+++	+	+
7. Depersonalisation	++	+++	+	+++
8. Emotional reaction				
a. euphory	+	—	++	+++
b. anxiety	—	++	—	+
9. Autism	—	—	—	+++
10. Language changes	—	+	+++	+

As can be seen, the different symptoms were not equally apparent in every case.

(1) The vegetative symptoms in mescaline and LSD-25 preceded the other symptoms, while in the case of the tryptamine derivatives the sensory disturbances appeared as early as the vegetative symptoms began.

(2) An interesting phenomenon observed only in the tryptamine derivatives was the appearance of atetoid, choreiform compulsive movements. As far as I know, these symptoms have not yet been described in the case of other hallucinogenic substances.

(3) The perceptual disturbances are qualitatively the same for all the substances; only quantitative differences could be observed.

(4) The emotional reactions, however, were qualitatively different, *viz.* my reaction to mescaline and DMT was euphoric, to the LSD-25 anxious, but in the case of T-9 euphoria and anxiety alternated. These phenomena, together with the severe autism and the above-mentioned ambivalency were observed only in T-9. However, it is well-known from the literature that it can occur in the case of mescaline and LSD-25 also (HUXLEY¹⁴, SOLMS²³).

The comparison shows that the structure of a model psychosis, which can be considered as a form of the acute exogen reaction type (BONHOEFFER), depends on the chemical structure of the causative agent, apart from the fact that absorption, metabolic and excretion processes may determine the course in time.

BIOCHEMICAL INVESTIGATIONS

The rapid onset and the short duration of the symptoms in the DMT-induced state is very interesting from a biochemical point of view, and it is probably connected with the rapid metabolism of DMT (FISH *et al.*).

We know from the investigation of ERSPAMER⁶ that in rats the main breakdown product of DMT is 3-indolylacetic acid (3-IAA) which is excreted in the urine partly in free form, but largely bound to glyocol as indolaceturic acid. We investigated the excreted indole derivatives in the human volunteers chromatographically and photometrically, and obtained the same results as ERSPAMER (SZÁRA²⁵). In addition, an interesting phenomenon was observed (Table III). We found in the urine after a larger dose of DMT more 5-hydroxyindolylacetic acid (5-HIAA) excreted than was normally present. Unchanged DMT was not estimated in the urine extracts. These data suggested

TABLE III
THE APPROXIMATE AMOUNT OF TOTAL 5-HIAA EXCRETED IN A 6 h PERIOD BEFORE
AND AFTER THE DMT EXPERIMENT

No.	Dose of DMT	Amount of 5-HIAA*	
		after expt.	before expt.
1	150 mg	1.6 mg	3.0 mg
2**	150 mg	1.2 mg	3.0 mg
3**	75 mg	1.5 mg	1.2 mg
4**	60 mg	2.0 mg	1.5 mg

* Estimated by two-dimensional chromatography, developed with *p*-dimethylamino-benzaldehyde, and the eluted spots measured colorimetrically.

** Self-experiments.

References p. 466.

that the DMT is very rapidly metabolized, and perhaps displays its effects by means of serotonin. In order to obtain more information about the relationship in the blood, I made an experiment with 60 mg DMT. The extracts of 15 ml blood taken before, and 10, 30 and 90 minutes after the experiment, were chromatographically investigated, and I found qualitatively only two indol derivatives, namely tryptophan and 3-IAA, but no serotonin 5-HIAA or unchanged DMT could be demonstrated. The 3-IAA level of the blood was elevated in the 10th and 30th minute (Fig. 3).

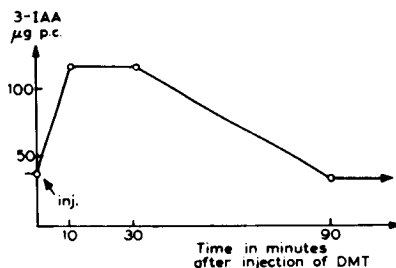


Fig. 3. The 3-IAA level of blood during the DMT experiment.

This finding did not support the presumption that serotonin plays a role in the psychotic effect of tryptamine derivatives. The evidence, however, is not sufficient to allow one to draw definite conclusions in this respect.

DISCUSSION

In discussing the mechanism of action of tryptamine derivatives, it must be admitted that at present there is no definite knowledge about the biochemical mechanism of action. The clinical picture, however, taking the other experiments on normal volunteers also into consideration, enables us to give some information concerning this mechanism.

The rapid onset of the psychotic symptoms makes it seem probable that DMT affects directly those brain structures that are affected indirectly by LSD and mescaline (BLOCK²). The appearance of choreiform athetoid movements is possibly due to an effect on structures other than those affected by LSD or mescaline. The tryptamine derivatives seem to be the first hallucinogenic substances to cause athetoid movements, and should therefore provide a new tool for investigating experimentally the exact mechanism of this phenomenon.

Unfortunately, I have not enough time to develop in detail the very interesting psychopathological symptoms of T-9, which reminded me of the conception of the "schizophrene Grundstimmung", described by WYRSCH²⁷.

It is, however, very remarkable that tryptamine derivatives without the OH-group in the 5-position are able to produce mental phenomena. As UDENFRIEND *et al.* demonstrated in animal tissues, there is no enzyme that could decarboxylate tryptophan to produce tryptamine; it is assumed therefore that only the enteral bacteria can produce this substance.

There is a possibility that from this tryptamine the schizophrenic organism may produce hallucinogenic substances in the wrong way enzymically. It is noteworthy that Prof. BUSCAINO and his team⁴ recently presented evidence of a disturbance in the indole metabolism in schizophrenia. Further work in this field would be desirable.

SUMMARY

The psychotic effects of N,N-dimethyltryptamine (DMT) and N,N-diethyltryptamine (T-0) have been compared with the effects of mescaline and LSD-25.

The most outstanding features of DMT model psychosis are the rapid onset and the short duration of the symptoms. This may indicate a different mechanism of action from that of LSD and mescaline.

New symptoms appearing with both tryptamine derivatives are the choreiform athetoid movements. This phenomenon could be a new tool for investigating experimentally the mechanism of the extrapyramidal compulsive movements.

The psychotic effects of tryptamine derivatives supports the aminotoxic and indole theory of schizophrenia.

REFERENCES

- ¹ A. H. AMIN, T. B. B. CRAWFORD AND I. H. GADDUM, *J. Physiol. (London)*, 126, (1954) 596.
- ² W. BLOCK, *Z. physiol. Chem.*, 294 (1953) 1; *ibid.*, 294 (1953) 49; *ibid.*, 296 (1954) 1; *ibid.*, 296 (1954) 108.
- ³ V. M. BUSCAINO, *Quaderni acta neurol.*, (1953).
- ⁴ V. M. BUSCAINO, D. KEMALI, R. BAGNULO, *Acta Neurol. (Naples)*, 10 (1955) 547.
- ⁵ V. ERSPAMER, *Pharmacol. Rev.*, 6 (1954) 425.
- ⁶ V. ERSPAMER, *J. Physiol. (London)*, 127 (1955) 118.
- ⁷ H. D. FABING, *Am. J. Psychiat.*, 113 (1956) 409.
- ⁸ H. D. FABING AND J. R. HAWKINS, *Science*, 123 (1956) 886.
- ⁹ M. S. FISH, N. M. JOHNSON AND E. C. HORNING, *J. Am. Chem. Soc.*, 77 (1955) 5892.
- ¹⁰ M. S. FISH, N. M. JOHNSON, E. P. LAWRENCE, E. C. HORNING, *Biochim. Biophys. Acta.*, 18 (1955) 564.
- ¹¹ W. A. FREYBURGER, B. E. GRAHAM, M. M. RAPPORT, P. H. SEAY, W. M. GOVIER, O. F. SWOAP AND M. J. VANDER BROOK, *J. Pharmacol. Exptl. Therap.*, 105 (1952) 80.
- ¹² I. H. GADDUM AND A. HAMEED KHAN, *Brit. J. Pharmacol.*, 9 (1954) 240.
- ¹³ H. E. HIMWICH, *J. Nervous Mental Disease*, 127 (1955) 413.
- ¹⁴ A. HUXLEY, *The Doors of Perception*, London, 1954.
- ¹⁵ D. KEMALI, V. M. BUSCAINO AND R. BALBI, *Acta Neurol. (Naples)*, 11 (1956) 209.
- ¹⁶ D. KEMALI AND G. ROMANO, *Acta Neurol. (Naples)*, 11 (1956) 959.
- ¹⁷ H. LANGEMANN, *Schweiz. med. Wochschr.*, 85 (1957) 957.
- ¹⁸ F. J. NIEUWENHUYZEN, *Proc. Koninkl. Akad. Wetenschap, Amsterdam*, 39 (1936) (9).
- ¹⁹ I. H. PAGE, *J. Pharmacol. Exptl. Therap.*, 105 (1952) 58.
- ²⁰ I. H. PAGE, *Physiol. Revs.*, 34 (1954) 563.
- ²¹ E. ROTHLIN, A. CERLETTI, A. KONZETT, W. R. SCHALCH AND M. TAESCHLER, *Experientia*, 12 (1956) 154.
- ²² A. SAI-HALÁSZ, GY. BRUNECKER AND S. SZÁRA, *Psychiat. et Neurol.*, (in press).
- ²³ H. SOLMS, *Praxis*, 45 (1956) 746.
- ²⁴ M. E. SPEETER AND W. C. ANTHONY, *J. Am. Chem. Soc.*, 76 (1954) 6208.
- ²⁵ S. SZÁRA, *Experientia*, 12 (1956) 441.
- ²⁶ S. UDENFRIEND, C. T. CLARK AND E. TITUS, *J. Am. Chem. Soc.*, 75 (1953) 501.
- ²⁷ J. WYRSCH, *Die Person des Schizophrenen. Studien zur Klinik, Psychologie. Daseinweise*. Paul Haupt, Bern, 1949.

DISCUSSION

A. SAI-HALÁSZ, *Istituto Centrale per le malattie Nervose e Mentali, Budapest (Ungheria)*
 Il collega SZÁRA ha avuto occasione stamane di parlare in dettaglio sugli esperimenti fatti con me con la dimetiltryptamina in soggetti normali. Ora vorrei richiamare l'attenzione soltanto su un fenomeno, che mi sembra assai interessante dal punto di vista clinico. Su 30 persone esaminate 22, cioè il 73% avevano sintomi semilateralizzati: le illusioni e le allucinazioni, i disturbi dello schema corporeo e dello spazio, i movimenti atetosici ed anche i segni di lesioni piramidali prevalevano a

sinistra. Questa differenza era netta. Per esempio un soggetto sperimentale guardando la mano sinistra diceva che essa non gli apparteneva più, aveva cambiato forma ed era divenuta luminosa e bellissima; guardando invece la mano destra, diceva che non presentava nulla di straordinario. Abbiamo sperimentato su tre persone mancine, e in questa i fenomeni prevalevano alla parte destra. Si dovrebbe concludere che la dimetiltriptamina produce una lesione semilateralizzata dell'emisfero non dominante del cervello.

Questo fenomeno finora non segnalato dalla letteratura per gli altri farmaci psicotropi ci propone due questioni:

(1) La prima sarebbe la seguente: come si può immaginare, che una sostanza chimica abbia un effetto nocivo molto più forte sull'emisfero cerebrale non dominante? Sappiamo al contrario, che è appunto l'emisfero dominante il più sensibile, specialmente se danneggiato nel sistema vascolare.

(2) La seconda domanda è di carattere psicopatologico. Si tratta cioè di sapere se questa semilateralizzazione ci può dire qualcosa sugli aspetti delle psicosi sperimentali. HOFF e PÖTZL hanno già dimostrato collo "Zeitrafferphänomen", che lesioni organiche dell'emisfero non dominante possono produrre fenomeni psicopatologici molto strani. Lo "Zeitrafferphänomen" è stato descritto già da BERINGER nel corso di psicosi sperimentali mescaliniche. Secondo la nostra opinione sarebbe di grande interesse studiare ancora le psicosi sperimentali già conosciute, al fine di evidenziare se ci sono differenze fra le due parti del corpo. Ci pare probabile, che questo fenomeno non sia un effetto solo della dimetiltriptamina. Ad ogni modo, conoscendo i fatti suddetti, noi possediamo ora una nuova sostanza per aiutarci a conoscere meglio i problemi dell'emisfero cerebrale non dominante.