DMT AT FIFTY*

STEPHEN SZÁRA

DMT-KUTATÁS AZ ÖTVENES ÉVEKBEN

A közlemény az N.N-dimetil-triptamin (DMT) hallucinogén hatásának 50 évvel korábbi fölfedezését írja le. A további tudományos kutatást nagyban hátráltatta az a körülmény, hogy az 1960-as években, főleg Amerikában, az illegális használat miatt törvényesen megszoritották a kutatási használatát. Jóllehet az állati és emberi szervezet képes DMT-t termelni, a klinikai tanulmányok nem tudták bebizonyitani, hogy ez hozzájárulna a szkizofrénia etiológiájához. További kutatás szükséges a DMT valószínű neuromodulátori szerepének tisztázására, ami később újabb terápiás módszerek kidolgozásához vezethet.

KULCSSZAVAK: DMT, dimetil-triptamin, hallucinogén, neuromodulátor, pszichoterápia, szkizofrénia

SUMMARY

The steps taken for the discovery of the hallucinogenic effects of N.N-Dimethyl-tryptamine (DMT) is described. DMT had a difficult first 50 years in medical research primarily for legal reasons as it was classified as one of the "drugs of abuse" by authorities in the USA and by the World Health Organization. It has not proved to be a "schizotoxin" as it was first suspected, but the book is not closed on its potential role in some other, high level function as an endogenous neuromodulator. Further clinical work may even substantiate its usefulness in therapeutic application, such as an adjunct to psychotherapy, perhaps not by itself, but in a modified form, or in combination with other substances.

KEYWORDS: anxiety, ayahuasca, bufotenin, cohoba, DMT, dimethyl-tryptamine, endogenous, euphoria, hallucinogen, ketamine, Largactil, LSD, mescaline, neuro-modulator, psilocybin, psychotherapy, receptor, Ritalin, schizophrenia, schizotoxin, serotonin

I would like to describe in some details the circumstances 50 years ago that has lead to our discovery of the hallucinogenic properties of N,N-Dimethyl-tryptamine (DMT) and review the history of DMT research in those years.

PRELIMINARIES

Maybe I will have to go back to even earlier times in 1953, when I, somewhat reluctantly, accepted the assignment to organize a Laboratory of Biochemistry at "Lipótmező" in Budapest. I said "reluctantly" because I was previously an assistant professor at the Department of Biochemistry of the Medical School, working with proteins and polysaccharides, and I wasn't sure if we could learn anything useful from molecules that would be relevant to mental illness. I was, however, persuaded by my new colleagues that very recently at least three events occurred in psychiatry that suggested some encouraging clues that chemistry may be indeed relevant. One was the introduction of a chemically well defined drug: chlorpromazine (Largactil) into the treatment of chronically ill schizophrenic patients with remarkable success (Delay & Deniker, 1955). The second was the discovery of LSD by Albert Hofmann ten years previously (Stoll & Hofmann 1943; Stoll 1947). The extreme potency of this drug (as little as 50 mcg) is producing symptoms in man that was held remarkably similar to naturally occurring psychoses. This suggested a very selective interaction with a specific receptor site somewhere in the brain. The third event was the appearance of an article in the Journal of Mental Science in 1954 (Hoffer, Osmond, and Smythies 1954) which pro-

* Presented at the IX. Hungarian Psychopharmacological Congress (Tihany, 2006)

posed a new theory of schizophrenia postulating a chemical agent, a "schizotoxin" with a chemical structure similar to serotonin. Perhaps a fourth event should be also mentioned that was not a scientific publication, nevertheless became very influential in psychiatric and psychological thinking about hallucinogenic drugs and mental illness: it was Aldous Huxley's 1954 book: The Doors of Perception (Huxley 1954).

To get started in the laboratory in 1953, we set up with Dr Katalin Szilágyi some chemical assays for the determination of indole-based substances in the serum of patients with various diagnostic categories hoping to find some correlations between indole content and diagnosis. While this was going on, sometime in 1955 I have read Huxley's new book "The Doors of Perception" and was quite intrigued by his description of the effects of mescaline. So much so, that I decided to get some mescaline to experience its effect myself and tried it at the end of 1955. I thought that it was absolutely essential to experience personally the effects of a known hallucinogen before I could consider doing research with this class of substances. I was glad that I tried it, as my experience was, in many ways, different from what I have read in the Doors of Perception. I became convinced that about 90 percent of the content of the book can be attributed to Aldous Huxley as a writer, and only 10 percent to the drug, mescaline.

While contemplating what could we do for research in this area, I have read somewhere, that the Sandoz Pharmaceutical Company in Basel, Switzerland was making LSD available to those who are interested doing scientific research with the substance. I have written an official letter requesting a few milligrams for research, but when the reply came, they simply said that they are sorry, but they cannot send me any LSD.

THE INSPIRATION

All this happened still in 1955. I was regularly scanning the scientific and clinical literature for any leads that might guide me to a new direction. In the hospital we had mostly clinically oriented journals, but I also frequently went back to the library of the Department of Organic Chemistry, where I did my doctoral thesis work, and found a fascinating article in the November issue of the Journal of the American Chemical Society (Fish, Johnson and Horning, 1955). The authors have found DMT and bufotenin (among others) in a snuff-powder, called "Cohoba", which was used by native Indians in South-America, Haiti, and Puerto Rico in their religious ceremonies. This article suggested that bufotenin might be the psychoactive ingredient but they did not know whether DMT was active or not. Apparently nobody else did, so I decided to start a project for testing it. First I had to have the compound itself. So I went back to my old lab, where I did my thesis work in organic chemistry and my colleague and friend, Miomir Mészáros allowed and helped me to synthesize about 20 grams of DMT and half a dozen homologues of it.

CLINICAL STUDIES IN BUDAPEST

Then I went to the director at my working place at the National Institute for Mental and Nervous Diseases in Budapest, Dr. Gimesné, Lili Hajdu who, after a review of the project by the Hospital's Medical Review Board, gave me permission to do the required preclinical and clinical studies. In this I was joined by three other psychiatrists András Sai-Halász, Zoltán Böszörményi, and Györgyi Brunecker who helped me to recruit, and test about 30 volunteers. In agreement with my coworkers, I sent in a short, preliminary report to the Swiss journal Experientia in the summer of 1956 before the Hungarian Revolution happened (Szára, 1956). The full reports appeared only two years later (Sai-Halász, Brunecker and Szára, 1958; Böszörményi and Szára, 1958). The effects of a medium effective dose (0.7 mg/kg) given intramuscularly, were similar to those of mescaline and LSD: visual illusions and hallucinations, distortion of body image, speech disturbances, and mood changes: euphoria or anxiety (depending on set and setting). The most remarkable aspect of the effects was the rapid onset (2-5 minutes) and short duration (30-60 minutes). These effects have been replicated by a number of independent groups of investigators (Turner and Merlis 1959; Rosenberg et al 1963; Gillin et al, 1976; Strassman et al 1994).

CLINICAL STUDIES IN WASHINGTON

When I moved to the American National Institutes of Health (NIH) in 1957 I had the good fortune to spend some years working with Julius Axelrod and others at the Clinical Center on the metabo-

lism of DMT and its homologues in normal volunteers and schizophrenic patients (Szára and Axelrod 1959; Szára 1961; Szára et al 1962; Szára 1964; Szára 1966; Szára et al 1966; Weil-Malherbe and Szára 1971). When in 1965 research with LSD and other hallucinogens were severely restricted in the U.S.A. I have expressed my dismay and concern in an article in the American Journal of Psychiatry that achieved some notoriety and the article recently became widely available on the internet (Szára 1967). In spite of the legal restrictions we managed to run a small (12 patients) study using N.N-diethyltryptamine (DET) as adjuncts to psychotherapy in chronic alcoholic patients in Washington (Faillace, Vourlekis and Szára 1967; Faillace, Vourlekis and Szára 1970) and we encouraged Stan Grof and his group in Baltimore to do a larger similar study on 50 patients using another homolog N,N-dipropyltryptamine (DPT) (Grof et al 1973; Soskin 1975).

CLINICAL STUDIES ELSEWHERE

For the last 30 years research with DMT (along with LSD and other hallucinogens) was slowed significantly by the Congressional Amendment of 1965 and by the Controlled Substances Act of 1970 by the United States Congress that classified the major hallucinogens as Schedule-I substances. In spite of these restrictions Rick Strassman at the University of New Mexico managed to obtain permission to conduct a clinical study of intravenously administered DMT in volunteers and studying the neuroendocrine, autonomic, and cardiovascular effects, in addition to recording their subjective reactions to the drug (Strassman and Qualls 1994; Strassman et al 1994). They also reported on tolerance developing to the physiological but not to the psychological effects to repeated doses of DMT (Strassman et al 1996). The only other clinical study using DMT in the last thirty years was reported only recently by Gouzoulis-Mayfrank and his colleagues from the University of Cologne, Germany (Gouzoulis-Mayfrank et al 2006). They have compared DMT with (S)-ketamine in a double-blind, cross-over study and claiming that both drugs produced global psychotic-like symptoms of the same intensity, but the phenomena, resembling positive symptoms of schizophrenia (thought-disorders or inappropriate affect) were stronger after DMT while those, resembling negative symptoms (attention deficits, motor phenomena) were stronger after (S)-ketamine. This study came to somewhat similar conclusions that Vollenveider (Psychiatric University Hospital, Zurich) has obtained in his comparison study with psilocybin and ketamine (Vollenweider 1994).

Since DMT is still a controlled substance and it is difficult to obtain permission to do clinical research on its effects, some researchers have turned to study the effects of Ayahuasca, a Brazilian native "tea" that contains DMT as its major psychoactive ingredient, and is used legally as a sacrament in religious ceremonies. Investigators, such as Dr. Ede Frecska and his collaborators are studying the effects on its users by measuring a high level perceptual function (binocular rivalry) (Frecska et al 2003 and 2004). There are a few other groups in the USA, Brazil, Spain and probably elsewhere that are also studying ayahuasca by some other means (Riba et al 2006; McKenna 2004; Stuckey et al 2005; Da Silveira et al 2005). Even more recently a study with psilocybin (a close relative of DMT) was published on the internet on July 11, 2006 (Griffiths et al, 2006). This article reported the results of a double blind, between–group, crossover study of psilocybin (30 mg/70 kg) vs. Ritalin (methyl-phenidate) (40 mg/70 kg) and the effects evaluated using established psychological scales. The results showed that 61% of the 36 subjects had a "full mystical experience" and 2/3rd of them rated their psilocybin experience as either the single most meaningful experience or among the top five most meaningful experiences of their lives.

PRECLINICAL STUDIES

I would like to add briefly that, in addition to the above mentioned clinical studies in the past 50 years, there was a large volume of pre-clinical research that has been conducted with DMT and its congeners. We ourselves have done some animal behavioral, and biochemical studies that focused on the interaction of these drugs with the serotonin system in the brain (Szára, Hearst, and Putney 1962; Szára 1962, 1964, 1968). Other, similar preclinical studies are reviewed by Domino (1974) and Aghajanian's group (Aghajanian and Haigler 1975; Aghajanian and Marek 1999). In one of our studies (Szára 1968) we reported a surprising finding in mice, using tritium (3H) labeled 5HTP, that LSD and DET (but not of their non-hallucinogenic

analogs) produced selective increases in the level of labeled serotonin in two areas: the Substantia Nigra and the Colliculus Anterior, while a selective decrease was produced in the Nucleus Vagus. This was surprising because, at that time, most everybody was betting on the neocortex as the location for the interaction between hallucinogens and serotonin, but only few were looking in the brainstem (Aghajanian and Haigler 1975; Aghajanian and Marek 1999). Today, however, the intimate interactions between cortex and brainstem nuclei, and the role of various subtypes of serotonin and other receptors in these interactions are more appreciated (Lin and Glennon 1994; Nichols 2004), so a reexamination of my earlier findings may be in order. Perhaps the relatively recent identification and cloning of the human indolethylamine N-methyltransferase enzyme could also help in this reexamination (Thompson et al 1999).

DMT: MODEL OF SCHIZOPHRENIA

The first half of the history of DMT may be characterized as the period, when the focus of research was guided by the "psychotomimetic" or "hallucinogenic" paradigm which is, in effect, proposing that these drugs are producing an experimental or model psychosis (Hoffer, Osmond and Smythies, 1954). Among the dozen or so proven or suspected natural hallucinogens DMT is probably the only one that could also arise in the human body as the methylated derivative of tryptamine, the decarboxylated product from tryptophan. Tryptamine itself is normally present in the brain (Martin et al 1972). An enzyme that can methylate tryptamine was first found in the lung of rabbits (Axelrod, 1962) and later also in the brain of both animals and humans (Saavedra and Axelrod 1972; Saavedra, Coyle and Axelrod 1973; Mandell and Morgan 1971). Numerous laboratories reported finding DMT in the blood and urine of some but not all schizophrenic patients and also in some other patients and even in normal subjects (Reviewed in Gillin et al 1976). This review comes to the conclusion, that "synthesis of DMT in man has yet to be demonstrated" and that the evidence for the role of DMT in schizophrenia is "currently incomplete". This pessimistic view, however, is not shared by everybody in the field and further research needed to clarify this issue. Further clinical work may also substantiate DMT's potential usefulness as an adjunct to psychotherapy, perhaps not by itself, but in a modified form, or in combination with other substances.

The Author is Retired Chief of Biomedical Branch at the National Institute on Drug Abuse. He is Emeritus Fellow of ACNP and CINP, member of AAAS, American Society of Pharmacology and Experimental Therapeutics, and member of the Scientific Advisory Board of the Heffter Research Institute. He was elected Honorary Member of the Hungarian Association of Psychopharmacology (2007). He is also recipient of ADAMHA Administrator's Meritorious Achievement Award (1984) and the Kováts Medal of Freedom from the American Hungarian Federation (2005).

Current address:
Stephen Szára
10901 Jolly Way, Kensington, MD, U.S.A.
E-mail: siszara@earthlink.net

IRODALOM

Aghajanian, G.K., Haigler, H.J. (1975): Hallucinogenic indoleamines: Preferential action upon presynaptic serotonin receptors. Psychopharmacol Commun 1(6):619-29.

Aghajanian, G.K., Marek, G.J. (1999): Serotonin and hallucinogens. Neuropsychopharmacology. 21 (2 Suppl): 16S-23S. Review.

Barbosa, P.C, Giglio, J.S, Dalgalarrondo, P. (2005): Altered states of consciousness and short-term psychological after-effects induced by the first time ritual use of ayahuasca in an urban context in Brazil. J Psychoactive Drugs. 37(2):193-201.

Böszörményi, Z., and Szára, S. (1958): Dimethyltryptamine experiments with psychotics. J. Ment. Sci. 104: 445-453.

Da Silveira, D.X, Grob C.S, de Rios, M.D, Lopez, E, Alonso, LK, Tacla, C, Doering-Silveira, E. (2005): Ayahuasca in adolescence: a preliminary psychiatric assessment. J Psychoactive Drugs. 37(2):129-33.

Delay, J., and Deniker, P. (1955): Neuroleptic effects of chlorpromazine in therapeutics of neuropsychiatry. J Clin Exp Psychopathol 16(2):104-12.

Faillace, L., Vourlekis, A., and Szára, S. (1967): Clinical evaluation of some hallucinogenic tryptamine derivatives. J Nerv Ment Dis 145, 306-313.

Faillace, L., Vourlekis, A., and Szára, S. (1970): Two-year follow-up of chronic alcoholics treated with hallucinogenic drugs. Comprehensive Psychiatry, 11, 51-56.

Fish, M.S., Johnson. N.M., Horning, E.C. (1955): Piptadenia Alkaloids Indole bases of P. Peregrina (L.) Benth. and Related Species. J. Am. Chem. Soc., 77:5892-5895.

Frecska E, White K.D, Luna L.E. (2004): Effects of ayahuasca on binocular rivalry with dichoptic stimulus alternation. Psychopharmacology (Berl). 173(1-2):79-87. Epub 2004 Jan 8.

Frecska E, White K.D, Luna LE. (2003): Effects of the Amazonian psychoactive beverage Ayahuasca on binocular rivalry: interhemispheric switching or interhemispheric fusion? J Psychoactive Drugs. 35(3):367-74.

Griffiths R.R. et al. (2006): Psilocybin can occasion mystical-type experiences having substantial and sustained personal meaning and spiritual significance. Psychopharmacology 2006; DOI.1007/s00213-006-0457-5.

Gillin, J.C., Kaplan, J., Stillman, R., and Wyatt R.J. (1976): The Psychedelic Model of Schizophrenia: The Case of N.N-Dimethyl-tryptamine. Am. J. Psychiatry 133: 203-208.

Gouzoulis-Mayfrank, E., Heekeren., Neukirch, A., Stoll, M., Stock, C., Dauman, J., Obradovic, M., and Kovar, K.A. (2006): Inhibition of return in the human 5HT2A agonist and NMDA antagonist model of psychosis. Neuropsychopharmacology. 31:431-441.

Grof, S., Soskin, R.A., Richards, W.A., and Kurland, A.A. (1973): DPT as an adjunct in psychotherapy of alcoholics. Int. Pharmacopsychiatry 8:104-115, 1973.

Hoffer, A., Osmond, H. and Smythies, J.R. (1954): Schizophrenia: a New Approach II. J. Mental Sci. 100:29-45.

Huxley, A.L. (1954): The Doors of Perception. Harper and Brothers, New York, NY.

Lin, G.C., and Glennon, R.A. (Eds) (1994): Hallucinogens: an Update. NIDA Research Monograph #146. Rockville, MD, National Institute on Drug Abuse.

Mandell A.J., and Morgan, M (1971): Indole(ethyl)amine N-methyl-transferase in human brain. Nature 230:85-87.

Martin, W.R., Sloan, J.W., Christian, S.T., and Clements, T.H. (1972): Brain levels of tryptamine. Psychopharmacologia (Berl), 24: 331-346.

McKenna D.J. (2004): Clinical investigations of the therapeutic potential of ayahuasca: rationale and regulatory challenges. Pharmacol Ther 102(2): 111-29.

Riba J, Anderer P, Jane F, Saletu B, Barbanoj M.J. (2004): Effects of the South American psychoactive beverage ayahuasca on regional brain electrical activity in humans: a functional neuroimaging study using low-resolution electromagnetic tomography. Neuropsychobiology. 50(1):89-101.

Riba, J., Romero, S., Grasa. E., Mena, E., Carrio, I., Barbanoj, M.J. (2006): Increased frontal and paralimbic activation following ayahuasca, the pan-Amazonian inebriant. Psychopharmacology (Berl). 186(1):93-98. Epub 2006 Mar 31.

Rosenberg, D.E., Isbell, H., Miner, E.J. (1963): Comparison of placebo, N-dimethyltryptamine, and 6-hydroxy-N-dimethyltryptamine in man. Psychopharmacology 4:39-42.

Saavedra, J.M., and Axelrod, J. (1972): Psychotomimetic N-methylated tryptamines; formation in brain in vivo and in vitro. Science 172:1365-1366.

Saavedra, J.M., Coyle, J.T., and Axelrod, J. (1973): The distribution and properties of the non-specific N-methyltransferase in brain. J. Neurochemistry 20:743-752.

Sai-Halász, A., Brunecker, G., and Szára, S. (1958): Dimethyltryptamine: Ein neues Psychoticum. Psychiatria et Neurologia, 135:285-301, 1958.

Soskin, R.A. (1975): Dipropyltryptamine in Psychotherapy. In Masserman, Jules H. (Ed): Current Psychiatric Therapies V.15:147-156.

Stoll, A and Hofmann, A. (1943): Partialsynthese von Alkaloiden vom Typus des Ergobasins. 6. Mitteilungen über Mutterkornalkaloide. Helvetica Chimica Acta 26: 944.

Stoll, W.A. (1947): Lysergsäure-diäthylamid, ein Phantasticum aus der Mutterkorngruppe. Schweiz Arch Neurol Psychiat 60:279.

Strassman, R.J., Qualls, C.R. (1994) Dose-response study of N,N-dimethyltryptamine in humans: I. Neuroendocrine, autonomic, and cardiovascular effects. Arch Gen Psychiatry 51:85-97.

Strassman, R.J., Qualls, C.R., Uhlenhuth, E.H., Kellner, R. (1994) Dose-response study of N,N-dimethyltryptamine in humans: II. Subjective effects and preliminary results of a new rating scale. Arch Gen Psychiatry 51:98 108.

Strassman, R.J., Qualls, C.R., and Berg, L.M. (1996): Differential tolerance to biological and subjective effects of four closely spaced doses of N,N-dimethyltryptamine in humans. Biol Psychiat 39:784-95.

Stuckey, D.E., Lawson, R., Luna, L.E. (2005): EEG gamma coherence and other correlates of subjective reports during ayahuasca experiences. J. Psychoactive Drugs. 37(2):163-78.

Szára, S (1956) Dimethyltryptamine. Its Metabolism in Man; the Relation of its Psychotic Effect to Serotonin Metabolism. Experientia, 12:441.

Szára, S. and Axelrod, J.: (1959): Hydroxylation and N-demethylation of N.N-dimethyltryptamine. Experientia, 15: 216.

Szára, S. (1961): Hallucinogenic effects and metabolism of tryptamine derivatives in man. Fed. Proc. 20, 885-888.

Szára, S., Hearst, E. and Putney, F. (1962): Metabolism and behavioral action of psychotropic tryptamine homologues. Int. J. of Neuropharm. 1: 111-117.

Szára, S. (1964): Effect of psychotropic tryptamine derivatives on the regional distribution of serotonin in the brain. In P.B. Bradley, F. Flugel, and P. Hoch (eds.): Neuropsychopharmacology. Amsterdam, Elsevier, 3:412-416.

Szára, S. (1966): Hallucinogenic amines and schizophrenia (with a brief addendum on N-dimethyltryptamine) in H.E. Himwich (ed.): Amines and Schizophrenia. Oxford, Pergamon Press, pp 181-197.

Szára, S., Rockland, L. H., Rosenthal, D. and Handlon, J. (1966): Psychological effects and metabolism of N.N-diethyltryptamine in man. Arch Gen Psychiat 15, 320-329.

Szára S. (1967): The hallucinogenic drugs - curse or blessing? Am J Psychiat 123, 1513-1518.

Szára, S. (1968): Brain serotonin, dehabituation and the hallucinogenic drugs. (Invited Discussion of Drs. G. Aghajanian and D. Freedman's Paper) In: Psychopharmacology, A Review of Progress. (D.H. Efron Ed. in Chief) PHS Publication No. 1836, pp 1195-1198.

Turner, W.J., end Merlis, S. (1959): Effects of some indolealkylamines in man. A.M.A. Arch. Neurol. Psychiat. 81: 121- 129.

Vollenweider, F.X. (1994): Evidence for a cortical-subcortical imbalance of sensory information processing during altered states of consciousness using positron emission tomography and [18F]fluorodeoxyglucose. In Pletscher, A and Ladewig, G., (Eds): 50 Years of LSD: Current status and perspectives of hallucinogens. New York and London. Parthenon.

Weil-Malherbe, H. and Szára, S. (1971): Biochemistry of functional and experimental psychoses. Monograph published in the Living Chemistry Series of C. C. Thomas, Springfield, Illinois.