

THE BIOLOGICAL ROLES OF HALLUCINOGENS: THEIR IDENTITY

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NOTES, WHAT IS THE ENDOGENOUS HALLUCINOGEN?

The secretion of an endogenous hallucinogen with the onset of labor is a characteristic of the model as presented above in the anecdotal, historical and biological arguments for the mother's (putative) state of raphe suppression. More than the identification of a particular agonist, the important issue is the nature of the receptor, which, by virtue of M's LSD effects, is taken to be serotonergic. Accordingly, among the five possibilities discussed below, serotonin itself (5-HT) must be considered as the birth factor along with the others.

As stated in the General Discussion of Part 2, 5-HT can elicit several "hallucinogen" effects that have been observed here and elsewhere, provided it is present at blood concentrations sufficient to produce "serotonin syndrome" or "serotonin toxicity". [5-HT] would be expected to rise during the mother's labor according to its well-known response to stress. However, the blood concentration means very little, whether normal (roughly 1 nanomole/ml) or elevated by 300%, to "toxic" levels. It is the local concentration among the brainstem areas of serotonergic function that is important, particularly the amount in the synaptic cleft and the raphe neuron dendrites. One tempting clue to the possibility of the parturition roles for 5-HT is the finding that [5-HT] increases as much as 1500% in the region of the rat hippocampus under the condition of imposed stress in rats (Linthorst et al, 2000). The relevance of this fact to parturition is that this increase requires mock stimulation of the hypothalamus by the addition of corticosteroid releasing factor (CRH). Since CRH secretion occurs naturally in parturition, [5-HT] could rise to a local level appropriate for functional binding to the 5-HT_{1a} and 2a receptors, especially as an increase above a normal stress response of 200 to 300%. Therefore, an argument can be made for 5-HT among the candidates for mediation of the roles of memory consolidation and fetal activation in the adult. Another consideration in favor of 5-HT in these birth aspects is the fact that serotonergic neurons are the sources of 5-HT that occupy the critical areas of raphe and limbic processes. However, the better case in favor of the

alternative endogenous hallucinogens is made below, mainly from evidence that these are endocrine substances unavailable to effects of blood factors.

The hallucinogens found in human tissue are: N,N-dimethyltryptamine (DMT), 5-methoxy-N,N-DMT, bufotenin (N,N-dimethylserotonin or 5-hydroxy DMT) and an oxidized form of epinephrine, adrenochrome. The most attractive candidate is dimethyltryptamine (DMT), known for at least fifty years as a drug detectable in body tissues (Barker et al, 2001). Interest in the late '60s was stimulated by the similarity between hallucinogenic effects and symptoms of schizophrenia, leading to the discovery of its synthetic enzyme, indoleamine methyl transferase in human blood plasma, urine and lung tissue. DMT is equal to LSD in potency and affinity for 5-HT_{2a} and 5-HT_{1a} receptors (Jacob and Shulgin, 1994; Strassman et al, 1994; Glennon et al., 1986). It is this similarity and the greater interest DMT provides for human studies (Strassman 1996) that favors its identification as the birth hallucinogen. However, the effective dose of 5-MeO-DMT as a hallucinogen is much smaller than that of DMT. Moreover, the preferred receptor for 5-MeO-DMT (in primates) is the 5-HT_{1a} (see Nichols 2004 p. 141). The following comments on DMT would apply to 5-MeO-DMT as well and either one or both might act as the birth hallucinogen. Further referral to these tryptamines will be written as DMT+.

Conceptually, the determination of whether or not DMT+ is secreted during late pregnancy and parturition seems simple enough. Syringes for withdrawing the parturient mother's blood would be pre-loaded with an inhibitor of monoamine oxidase (MAO) such as harmaline or pargyline. A plausible case for detecting DMT this way can be made, partly because of its low control background that occurs naturally. The amount of DMT is very small in all tissues and its half-life when injected is short (Kaplan et al, 1974), owing largely to its rapid oxidation by MAO-a. For this reason, a test for hallucinogens has to be quite sensitive, requiring methods sensitive to picomole amounts, e.g., isotope dilution of N,N-deuteriomethyl tryptamines (Barker et al, 2001) or by gas chromatography/mass spectrometry (Forsström et al, 2001). However it is done, this test conforms to the stringent demand for a good hypothesis, as a

negative result would destroy the RaRN hypothesis. The main problem with this test would be the detection of DMT+ in a complex biological fluid such as blood that may necessitate fractionation procedures, further diminishing DMT+ measurements.

Because DMT is elusive for reasons mentioned above, its source within the brain is yet to be established. Earlier and fascinating publications by Dr. Rick Strassman suggest that a likely source is the pineal gland, which is a most attractive possibility as the source for a number of good reasons:

- 1.. The gland is loaded with the precursor of both DMT and melatonin and contains all the enzymes necessary to synthesize DMT, 5' tryptophan hydroxylase, N,N-dimethyltransferase and O-methyltransferase (for 5-MeO-DMT).
2. The pineal is tucked within the central posterior midbrain, which is an excellent location for fast local delivery of DMT to the brainstem. This would minimize the exposure time of DMT to oxidation by monoamine oxidase a (MAOa). Also, an inhibitor of methyltransferase for DMT's N,N-dimethyl group is present in the gland (Narasimhachari et al, 1974). This sequestered arrangement insures against systemic effects of drugs on DMT such as MAOa inhibitors (see [3.] 1.4.4 "REM Sleep Heals Trauma). Otherwise, homeostatic balance in the brain would be lost from the systemic appearance of this powerful hallucinogen.
3. It is a nighttime gland, owing to its known function of secreting melatonin to promote sleep and to stop this secretion when the suprachiasmatic nucleus in communication optic nerve collaterals, perceives light. It could easily switch from melatonin synthesis to DMT synthesis to begin the REM sleep state as described previously ([3.] 1.4.4).
4. Bufotenin (5-hydroxy DMT) is found in pineal extracts and uterine tissue (van der Horst and Ebels 1980.) It is not unlikely that all three, DMT, 5-methoxyDMT and bufotenin are secreted in concert as a mixture in their postulated biological role in human parturition.

Thus, it is likely that a biological mechanism for liberating DMT synthesis and release may be found to link this hallucinogen to the pineal and to secretion during parturition. This is a research direction yet to be explored (Sandrock Jr. et al 1980).

DMT has been found in lung tissue after hyperventilation at rest, the same kind of breathing that begins naturally for the mother in labor. DMT's strongly hallucinogenic effect, if administered without a MAO inhibitor, lasts less than two minutes (Strassman et al., 1996). Much longer lasting influence requires MAO inhibitors such as those derived from plant preparations used as adjuncts to DMT in the ayahuaska ceremonies of South American shamans (Schultes RE et al., 2001 p 129). This is a lesson, since externally administered MAO inhibitors (MAOIs) cannot be said to affect endogenous DMT+ concentrations, since they do inhibit REM sleep, which is counter to expectations from results on REM stimulation by 5-HT_{1a} agonists ([3.] 1.4.4). This testifies to the sequestered nature of DMT in the brainstem. The action of LSD described in Part 2 of this monograph is the first demonstration of this drug as a pharmaceutical in the conventional sense. This same conventional pharmacology is by the dose-response character of DMT's autonomic effects (Strassman, et al., 1994).

References for “What is the Endogenous Hallucinogen?”

Barker SA, Littlefield-Chabaud MA, David C. (2001) Distribution of the hallucinogens N,N-dimethyltryptamine and 5-methoxy-N,N-dimethyltryptamine in rat brain following intraperitoneal injection: application of a new solid-phase extraction LC-APCI-MS-MS-isotope dilution method. *J Chromatogr B Biomed Sci Appl.* 2 Feb 10;751(1):37-47.

Forsström T, Tuominen J, Karkkainen J. (2001) Determination of potentially hallucinogenic N-dimethylated indoleamines in human urine by HPLC/ESI-MS-MS. *Scand J Clin Lab Invest.* 2001;61(7):547-56.

Glennon RA, Titler M, Young R. (1986) Structure-activity relationships and mechanism of action of hallucinogenic agents based on drug discrimination and radioligand binding studies. *Psychopharmacol Bull.* 22 953-8.

Jacob III P and Shulgin AT. (1994) www.nida.nih.gov/pdf/monographs/146.pdf

Narasimhachari N, Lin RL, Himwich HE. (1974)

Inhibitor of indolethylamine N-methyltransferase in pineal extract. *Res Commun Chem Pathol Pharmacol.*)1Oct;9(2):375-8.

Nichols DE (2004) *Hallucinogens Pharmacology & Therapeutics* 101 (2004) 131–181176

Sandrock Jr. AW, Leblanc GG, Wong DL, & Ciaranello RD (1980) Regulation of rat pineal hydroxyindole-O-methyltransferase: evidence of S-adenosylmethionine-mediated glucocorticoid control. *J Neurochem.* 1980 Sep;35(3):536-43.

Schultes RE, Hofmann A and Ratsch, C. 2001 “Plants of the Gods” Healing Arts Press, Rochester VT ISBN 0-98281-979-0

Strassman, R. J. (1996). Human psychopharmacology of N,N-dimethyltryptamine. *Behav Brain Res* 73, 121 – 124.

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., & Berg, L. M. (1996). Differential tolerance to biological and subjective effects of four closely spaced doses of N,N-dimethyltryptamine in humans. *Biol Psychiatry* 39, 784 – 795.

Strassman RJ (2001) *DMT: The Spirit Molecule* Rochester, VT: Park Street Press, 2001, 358 pp + xviii, \$16.95 pb *Journal of Near-Death Studies*

van der Horst CJ, Ebels I. (1980) Extraction of pineal and uterine tissue at different pH values: a preliminary report on the occurrence of a few groups of compounds in both tissues. *Cytobios.*;29(115-116):191-203.