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SP.236 / ESG.SP236 Exploring Pharmacology
Spring 2009

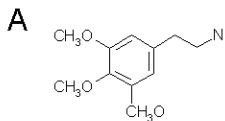
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N,N-Dimethyltryptamine and its Analogs

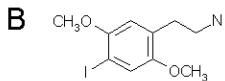
SP.236 Pharmacology Seminar

- 1 Preliminaries
 - Sources
 - Phenethylamines and Tryptamines
 - Serotonin-like Psychedelic Drugs, Receptor Chemistry
- 2 DMT
 - *N,N*-DMT
 - 5-MeO-DMT
 - Bufoteneine (5-hydroxy DMT)
 - Psilocybin (4-phosphoryl-DMT) and psilochin (4-hydroxy-DMT)

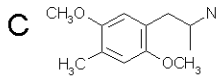
- *A Primer of Drug Action*, by Robert M. Julien
- *Psychedelics Encyclopedia*, by Peter Stafford
- *TiKHAL: Tryptamines i Have Known And Loved*, by Alexander and Ann Shulgin
- *The Neuropharmacology of Hallucinogens*,
<http://erowid.org>



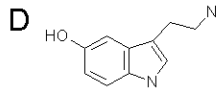
MESCALINE



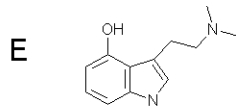
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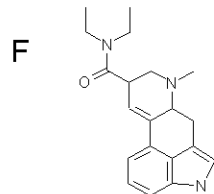
DOM



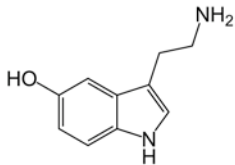
SEROTONIN



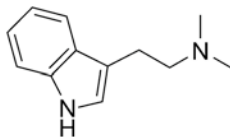
PSILOCIN



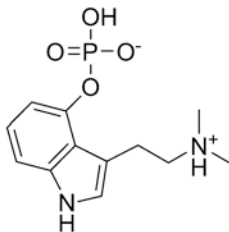
LSD



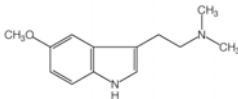
(a) 5-HT (Serotonin)



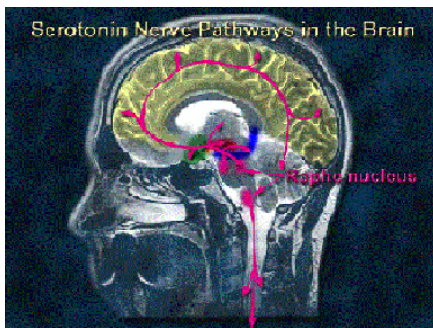
(b) *N,N*-DMT (DMT)



(c) 4-phosphoryl-DMT
(Psilocybin)



(d) 5-MeO-DMT



Additional speculation on major source of serotonin activity:

- Pontine (dorsal) raphe filters incoming sensory stimuli
- Eliminates “unimportant, irrelevant, or commonplace” sensations and perceptions flooding the body

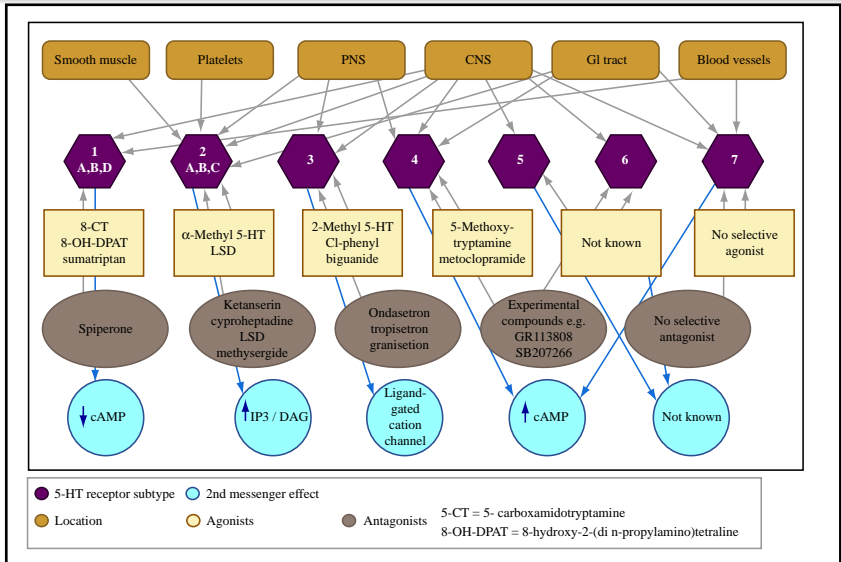


Figure by MIT OpenCourseWare.

- Structurally similar to 5-HT → Exert effects through interactions at 5-HT synapses.
- Specifics seem to be difficult:
 - Almaula: Binding and activation at 5-HT_{2A}
 - Pennington and Fox: Spectrum of antagonist/agonist effects at 5-HT receptor subtypes, particularly 5-HT_{1C}
 - Egan: Agonist action at 5-HT_{2C} and 5-HT_{2A}
 - Partial agonist with dopaminergic D₂ receptors

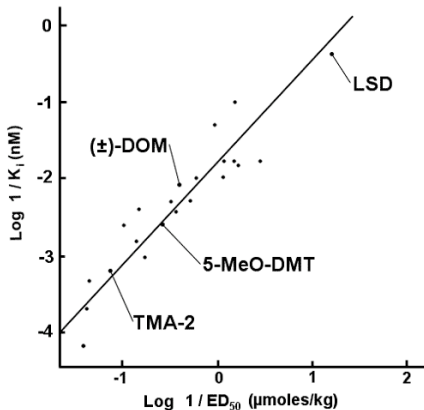


Fig 1. The affinity of various hallucinogens for the 5-HT₂ receptors correlates with the behavioural effect produced in a discrimination experiment. $r=0.938$.
Graph adapted without permission from Glennon et al., 1984.

- Like LSD-25, binds to serotonin 5-HT₂ receptors
- Metabolized by enzyme monoamine oxidase (MAO). Therefore when taken orally (rare), an MAOI is used.
- Strassman, et al.: Onset of action at 2 min, negligible at 30. Elevated blood pressure, heart rate, and temperature; dilated pupils, and increased endorphin and hormone levels.

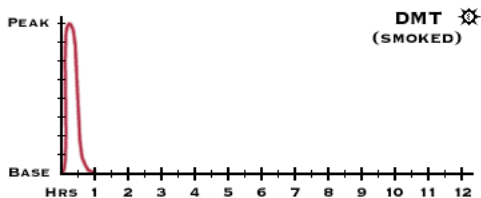
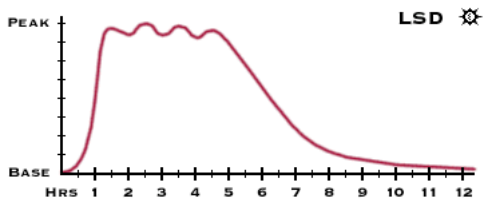
“[. . .] a rapidly moving, brightly colored visual display of images. Auditory effects were less common. ‘Loss of control’ associated with a brief, but overwhelming ‘rush,’ led to a dissociated state, where euphoria alternated or coexisted with anxiety. These effects completely replaced subjects’ previously ongoing mental experience and were more vivid and compelling than dreams or waking awareness.”¹

¹R. J. Stassman, C. R. Qualls, E. H. Uhlenhuth, and R. Kellner, *Archives of General Psychiatry* 51 (1994): 98-108.

- DMT, a schedule I drug, is an endogenous psychoactive; tryptamine metabolites are found in mammals
- Dreaming, near/death experiences (unsourced).
- Methyl transferase (for DMTs) found in lung, brain, liver, and heart.
- Potent inhibitor Pineal gland
- With an MAOI → serotonin (HIOMT) → 5-MeO-trypt (INMT) → 5-MeO-DMT.
- Candy bar + plants with 20-50mg harmine/harmaline = lots of 5-MeO-DMT (maybe).

- Native American plant ceremonies, such as Ayahuasca.
- Main active alkaloid in psychedelic snuffs

“Onset is fast and furious, sometimes compared to being launched from a cannon. It is a fully engaging and enveloping experience of visions (actual visual effects less common) which varies greatly from one individual to the next. Users report profound changes in ontological perspective, experiencing the void, the shattering of the universe, frightening and overwhelming forces, complete shifts in perception and identity followed by an abrupt return to baseline. Because of the nature and intensity of the experience, users are almost always seated or lying down with someone nearby to take the pipe as the experience begins. Unlike with N,N-DMT, few users report significant coherent visual effects.”



- Also a metabolite, which *might* be correlated with psychiatric disorders.
- Chemical constituent in the venom and eggs of several species of toads belonging to the *Bufo* genus.
- Bufo venoms also contain digoxin-like cardiac glycosides, and ingestion of the venom can be fatal.



(Bufo alvarius): Would you taste *this* frog?

- Mushrooms that grow pretty well in lots of places
- Eaten raw and last 6-10 hours
- Psilocybin metabolized to psilochin
- The time scale here is interesting...

“[. . .] It permits you to travel backward and forward in time, to enter other planes of existence, even to know God . . . Your body lies in the darkness, heavy as lead, but your spirit seems to soar and leave the hut, with the speed of thought to travel where it listeth, in time and space, accompanied by the shaman’s singing . . . At least you know what the ineffable is, and what ecstasy means. Ecstasy! The mind harks back to the origin of that word. For the Greeks, ‘ekstasis’ meant the flight of the soul from the body. Can you find a better word to do describe this state? ”²

²M. E. Crahan, *Bulletin of the Los Angeles County Medical Association* 99 (1969): 17.

Serotonin Nerve Pathways in the Brain

