Lysergic Acid Diethylamide. A Brief Review

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OBJECTIVE

- To make a general view of the main aspects related to LSD.
- To understand its pharmacokinetic and pharmacodynamic, making special attention in LSD's effects in the central nervous system (CNS).
- To know its undesirable effects.

CONTEXTUALIZATION

- **LSD**: semysinthetic product of lysergic acid, a natural substance from the parasitic rye fungus *Claviceps purpurea*.
- Synthesized for the first time in 1938 by the swish chemist Albert Hofmann.
- 1950s: offered to the medical community like an experimental tool to study temporary psychotic-like states in normal people.
- 1960s: began to be use as a recreational drug. Forbidden in EUA in 1967.
- Nowadays, is one of the most consumed drugs of abuse due to its low cost and easy obtaining.

MATERIAL AND METHODS

- Systematic search with the medical database PubMed.
- Keywords: "LSD", "LSD effect", "LSD pharmacodynamics", "LSD pharmacokinetics", "Hallucinogen compounds", "Serotonin", "5-HT_{2A} receptor".

CHEMICAL STRUCTURE

- Molecular formula: $C_{20}H_{25}ON_3$
- Molar mass: 323,42g/mol

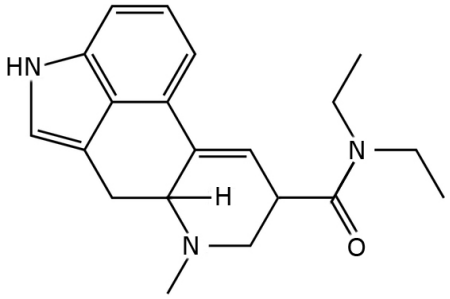


Figure 1 Chemical structure of LSD. It consists on an indole system with a tetracycline ring. Carbons 5 and 8 are asymmetric.

PHARMACOKINETIC

- Dose: optimum dosage 100-200µg → high potency.
- Administration: no qualitative differences regarding psychological effects independently of the administration's route.
- Absorption: after oral administration, completely absorbed in the digestive tract.
- Distribution: no data in human. LSD is able to penetrate the CNS.
- Metabolism and excretion:
  - Metabolized by liver enzymes into structurally similar metabolites.
  - Elimination half-life: 3,6h.
  - LSD metabolites detectable in urine until 4 days after administration.

PHARMACODYNAMIC

- The pharmacological basis of the stimulus produced by hallucinogenic compounds is **serotoninergic**.
- Receptors:
  - **5-HT_{2A}** serotonin receptor:
    - Main receptor mediating hallucinogens effects.
    - Widely expressed in CNS structures involved in psychosis.
    - G-protein coupled receptor. LSD acts as an agonist causing a dose-related inhibition of 5-HT neurons firing rate.

5-HT_{2A} activation → Phospholipase C (PLC) activation → PIP_2 hydrolysis → DAG → Protein kinase A (PKA) activation; IP_3 → ↑ Ca^{2+} intracelular

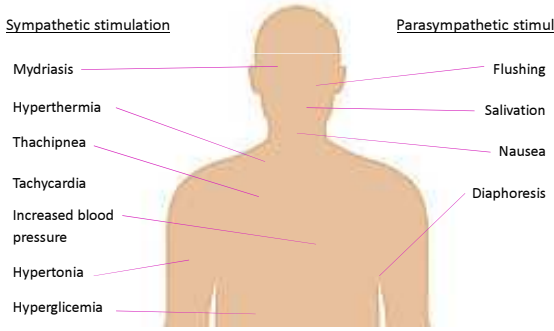
5-HT_{2A} activation → Phospholipase A2 (PLA2) activation → Arachidonic acid (AA) releaSe

  - **5-HT_1** serotonin receptor:
    - **5-HT_{1A}**: somatodendritic receptor, inhibit the firing of 5-HT neurons.
    - **5-HT_{1B}**: autoreceptors, inhibit serotonin release.
  - **5-HT_{2C}** serotonin receptor:
    - Located on non-5-HT neurons.
    - Operate via neuroanatomical circuits based on polysynaptic inputs to 5-HT neurons.
    - LSD acts as agonist. Its activation causes a dose-related inhibition of 5-HT neuron firing rate.
  - **D_2** dopamine receptor:
    - Responsible of the second phase of the clinical effects of LSD.
    - LSD acts as an agonist neuromodulating the decrease of extracellular glutamate in prefrontal cortex.

↑ glutamate → **HALLUCINATION**

Somatic effects

- Stimulation of both branches of the autonomic nervous system.



- Chronic administration leads to a neuroadaptative state.
- No evidence of physical consequences.
- No carginogenic potential.
- No documentend deatdh due to LSD intoxication.

Psychological effects

- Stimulation of affect (euphoria).
- Enhanced capacity of introspection.
- Perceptual changes:
  - Illusions
  - Hallucinations
  - Synesthesias
  - Alteration of thinking and time experience

CONCLUSIONS

- Lysergic acid diethylamide (LSD) is a semisynthetic product of lysergic acid. It is an ergoline consisting of an indole system with a tetracycline ring.
- The pharmacological basis of LSD's stimulus is serotoninergic. Its principal action takes places by the activation of 5-HT_{2A} receptor of the serotoninergic neurons in the raphe nucleus, were lysergic acid acts as an agonist inhibiting the 5-TH neurons firing rate. It also activates 5-H_{T1A} and 5-H_{T2C} receptors, acting again like an agonist and working in the same direction.
- D_2-like are activated by LSD as well, resulting in an increasing glutamate release. Glutamate release represents a final common pathway for the actions of serotoninergic and other hallucinogens.
- The psychological effects of LSD are characterized by an alteration of the state of consciousness. The main expression of them are the perceptual changes, where it highlichts the hallucinations.
- Autonomic changes produced by LSD reflect a stimulation of both sympathetic and parasympathetic branches of the autonomic nervous system.
- The main undesirable effect mediated by LSD's administration is the flashback, the reexperiencing of one or more of the perceptual symptoms experienced while the intoxication without the use of the hallucinogen.