Pharmacological Constituents of Mescaline & Salvinorin A

Preliminary Analysis

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"Sobriety diminishes, discriminates, and says no; drunkenness expands, unites, and says yes… no account of the universe in its totality can be final which leaves these other forms of consciousness quite disregarded"
--William James--

Anthropologists Carolyn Boyd and Philip Dering identified two hallucinogenic plants in **4,000-year-old cave paintings** near Pecos River, Texas: Images of spiny ovals attached to staffs closely resemble the seed pods of **jimson weed**, and the disk-shaped crowns of the **peyote cactus** are represented by dots and deer impaled by arrows.

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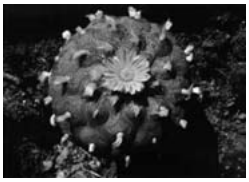
Peyote Cactus

- Lophophora williamsii:
- Relatively small and spineless
- Deserts of Mexico and S.W. United States
- Crowns sliced off and dried to form hard brown discs known as mescal buttons
- Buttons chewed and swallowed for hallucinogenic properties



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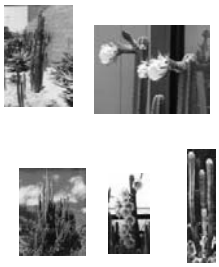
San Pedro Cactus

- Trichocereus pachanoi
- Andes: evidence of use in Peru over 3000 years ago
- Mescaline highly concentrated in skin, which is peeled, dried and made into a powder
- Natives boil slices of stem and drink the liquid



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San Pedro Varieties

- Trichocereus peruvianus cactus
- Other varieties of hallucinogens from same family

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Antiquity Of The Divine Cactus

- Centuries old (3000 years among Aztec) use throughout present day S.W. United States and N. Mexico
- Indigenous consumption believed to be connected with religious rituals: releases spirit and power is absorbed by user Peyote believed to be a **omnipotent medicine**
- Hernandez of the court of King Philip II of Spain first reported information about "strange herbs and medicines": **collected 1200 plants and first recorded visions and mental changes resulting from consumption**
- Spanish Catholic priests circa 1600's asked confession from native American converts of their peyote use: believed plant conjured demons

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Antiquity…

- First explored scientifically by German chemist Arthur Heffter who **isolated alkaloids from mescal buttons: self-experimentation for the sake of science**
- American psychologist Heinrich Kluver detailed mescaline phenomenology in 1928: published book entitled *Mescaline* which contained experiential data of the effects: **proposed that the drug be used as a research tool for uncovering the depths and unconscious dynamics of the human psyche**
- 1930's anthropologist Weston La Barre writes thesis on peyote, noting that the **essential goal of the native American Indian is to obtain visions for prophecy, curing, and inner strength**

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Antiquity…

- **Aldous Huxley** publishes *The Doors Of Perception* in 1954*:* **integrated the psychedelic experience into mainstream culture**; enormous advocate of the drug which he viewed as infinite in its significance
- **Native American Church (1918):** Preservation of peyote rituals instituted through intertribal organization to allow members to legally ingest peyote for religious purposes: one-quarter of a million members today.
- Apart from the above use, peyote is a **Schedule 1 controlled substance** that is illegal in all 50 states.

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Rituals

- Sacramental use not considered abuse
- Native participants surround fire: engage in trance-like state, intensified by a pulsating drumbeat or chanting
- Experience of achieving a vision through direct communication with spirits
- Tranquility

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Psychoactive Constancy

- Alkaloid mescaline: unprecedented presence: **longevity, stability, and psychoactive potential** over immense periods of time.
- Scientists recently unearthed and performed chemical analysis on **1000 year-old**, peyote buttons strung around the necklace of a skeletal corpse discovered in a Mexican burial cave, determining that the chemical constituents of the plant contained **psychoactive viability**.

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"Entheogen" Defined

- Literally means "generating the divine within": strictest sense refers to a **psychoactive plant or chemical substance taken to occasion spiritual or mystical experience**
- Looser definition: **non-addictive artificial and natural substances that induce alterations of consciousness** similar to those documented for ritual ingestion of traditional shamanic inebriants
- "Entheogen" replaces the judgment-laden misnomer "hallucinogen," and the culturally freighted term "psychedelic"
- 250 plant species produce controlled substances: hundreds more elicit psychoactive effect

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Hallucinogen

- Chemically and pharmacologically heterogeneous group of substances that have in common the potency to cause in the user a distortion of perception and a mental state resembling psychosis

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Classification: Hallucinogen

- Entheogenic Plant Source: Peyote: **Phenylalkylamine**
- **Phenethylamine** derivative

  Mescaline: categorical prototype both qualitatively and quantitatively of hallucinogenic substances

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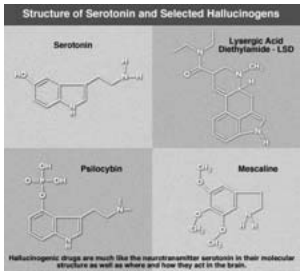
Mescaline Comparative Structural Resemblance



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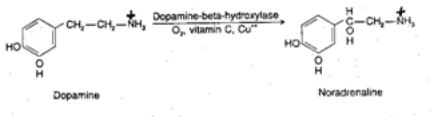
Nearest Mescaline Structural Similarity: Catecholamine NTs



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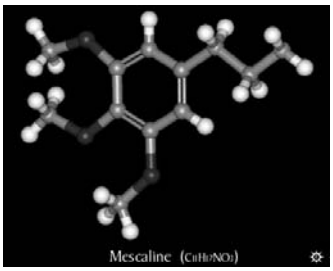
Mescaline Molecule



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Active Compounds of Mescaline

- **3,4,5 Trimethoxyphenylethylamine**
- **3,4,5 - trimethoxyphenylacetic acid**: main metabolite: similar to diamine oxidase
- Suggested that there exist 30 other psychoactive chemicals in peyote: inconclusive

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Chemical Specifics

- **NAME :**Mescaline
- **CHEMICAL NAME :**3,4,5-Trimethoxybenzeneethanamine
- **ALTERNATE CHEMICAL NAMES :**3,4,5-trimethoxyphenethylamine; mezcaline
- **CHEMICAL FORMULA**: C11H17NO3
- **MOLECULAR WEIGHT**: 211.26
- **MELTING POINT**: 183-186° C (Sulfate dihydrate)
- **LD50**: crystals : 212 mg/kg i.p.(mice)
- **LD50**: crystals : 132 mg/kg i.p. (rats)
- **LD50**: crystals : 328 mg/kg i.p.(guinea pigs)
- **From the Merck Index 12th Edition**

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Ontology of Drugs

- Biobehavioral changes are preceded by a combination of biochemical alterations and interaction with external environment, which essentially defines the experiential role of psychoactive drugs

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Admonishment

- Data extrapolation renders conclusion and even speculation about specific drug action unreliable
- "It is not easy to establish relationships among psychedelic drugs, neurotransmitters, brain activity, and states of consciousness. The brain is complex and inaccessible to delicate experimental manipulation by chemical means"

  Lester Grinspoon

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Discriminative Stimulus Properties of Mescaline

- Present and pervasive
- Diverse and various
- Uncertain and unpredictable
- Transitory and context-dependent
- Multiple receptor systems involved
- Compound discriminative stimuli influenced by a variety of factors experimental and others

  Dose, sensitization, etc.

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Pharmacokinetics: Hallucinogenic Context

- **ED50**: Variable
- **LD50**: Unknown
- Ratio of LD50 to ED50: **therapeutic index**: unknown/ N/A
- **Potency**: absolute number of molecules of drug required to elicit a response: extrapolated, variable
- **Efficacy**: Maximum effect obtainable in which additional doses produce no effect: unknown
- **Variability**: individual differences in drug response, with some persons responding at very low doses and some requiring much more drug

Of particular relevance with hallucinogens:

Set/ Setting/ Experience/ Expectations:

Subjective/ Behavioral Effects

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Pharmacokinetics

- **Ingested orally**: absorbed rapidly and completely in gastrointestinal tract
- **Hallucinations: 300 - 600 mg**

  20 mescal buttons: 600mg
  - **10-30 times lowest dose** producing behavioral effects may be **lethal**
  - Death in animals results from **convulsions and respiratory arrest**
  - Mescaline is **1000 - 3000 times less potent than LSD** and **30 times less potent that psilocybin**

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Pharmacokinetics…

- **Maximum concentration** in brain: 30 to 120 minutes
- Effects persist for up to **9 to 10 hours**
- Between **3.5 and 4 hours** after ingestion, mescaline produces an acute psychotomimetic state
- Hallucinations persist for about **2 hours** depending upon dose
- About half the dose is **excreted unchanged** after six hours
- Others suggest that it is not metabolized at all before excretion

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Pharmacokinetics…

- **Slow tolerance** builds with repeated administration
- **Cross-tolerance** with LSD
- Intoxication can be alleviated or stopped with chlorpromazine (**Thorazine**): tranquilizer or diazepam (**Valium**)
- Not antagonistic action however

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Brain Imaging

- A **hyperfrontal pattern with emphasis on right hemisphere activity**: questions validity of the concept of hypofrontality as an explanation for acute psychotic symptomatology
- Mescaline seems to selectively increase neuronal activity, especially in the striatolimbic system to the right hemisphere (as in schizophrenia)

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Physiological Effects: Usual Oral Dose 5 mg/kg

- **Sympathomimetic effects**: mimic the effects of norepinephrine or epinephrine
- Increase heart rate/ increase temperature
- Behavioral arousal/ trembling
- Nausea/ dizziness
- Heavy perspiration/ chills
- Dilation of pupils (mydriasis)
- Dry mouth
- Anxiety

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Physiological Effects…

- Mild ataxia (coordination and reflex disruptions)
- Hyperreflexia of limbs
- Muscle weakness/relaxation: sedation
- Vomiting
- Depressed heart rate,increase blood pressure (hypertension), respiratory rhythm, contract intestines and the uterus, cause headache, greater ataxia, dry skin with itching, and tremors in higher doses

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Contingent Psychic Effects

- Enhanced emotional responses
- Sensory-perceptual distortion: space and time
- Altered perception of colors, sounds, shapes, etc.
- Complex hallucinations: animals, people
- Dreamlike feelings
- Depersonalization
- Somatic effects: (tingling skin, weakness, tremor)
- Synesthesia: mixing of senses
- Euphoria: ecstatic state
- Otherwise sensorium is normal and insight retained!

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General Psychic Effects

- Dissolution of ego boundaries
- Visual hallucinations
- Dimensions of “oceanic boundlessness”
- Anxious passivity experiences

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Pharmacodynamics: Hallucinogenic Contingency

- **Placebo Effects**: significant reaction depending upon environment/ mental set:
- **Mechanisms**: conditioning, expectancy, self-liberation of endogenous neurotransmitters, particularly endorphins & adrenaline-like catecholamines.
- **Psychophysiological self-regulation** induced by powerful hallucinogens.

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Psychopharmacology

- **Medial forebrain bundle** in mesolimbic system: neurobiological site of action
- **Catecholamine neurotransmitters**: facilitative effect mediated by norepinephrine and dopamine systems
- **Nucleus accumbens**
- Evidence for the inhibition of **cholinergic** transmission by blocking release of acetylcholine.
- **Glutamatergic** transmission altered

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Catecholamine (Phenethylamine) Psychedelics

- Structural resemblance NE, DP, and the amphetamines: contain basic phenyl ring, an ethyl side chain with attached nitrogen or amine ring
- As variant as they are, these groups confer psychedelic properties: methoxylation of the benzene ring exerts amphetamine-like psychostimulant actions, presumably on dopaminergic and 5-HT2a receptor subtypes
- Psychedelic actions: full agonist action at post-synaptic serotonin 5-HT2a receptors
- Combination of catecholamine and serotonin actions points to a complex interaction between dopamine and serotonin, explaining their intermediate position between stimulants and LSD-like hallucinogens

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Implicated Neurotransmitters

- **Norepinephrine**: alpha and beta
- **Serotonin**: 5-HT2a; 5-HT2 receptor 6
- **Dopamine**
- **Glutamate**

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Norepinephrine Action: Beta Receptors

- Poised to **modulate memory, motor, and sensory functions**
- Most dense in the **hippocampus** (especially the CA1 region) where they influence data-processing functions
- NE activates Beta receptors, **initially slowing down cells** (due to the beta receptors suppression of spontaneous background firing)
- However, this brief inhibition is followed by **improvement of the signal-to-noise ratio (efficiency/strength) of the post synaptic cell**
- Ultimately: **Excitation**

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Norepinephrine Action: Beta Receptors…

- Waves of incoming impulses **stimulate the cell into stronger excitatory synaptic responses**
- Studies of behavior illustrate that **physiological constraints are soon placed on unrestrained excitability**
- Despite an increase in EEG response activity, the inherent side effects of excessive arousal act to **slow to individuals' behavioral reaction times**

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Norepinephrine Action: Alpha1-Receptors

- More direct approach: rather than the typical synaptic excitation of tens of milliseconds, excitation lasts for hundreds of milliseconds
- Once NE activates the A1-receptors; however, these **long-lasting A1 responses are not sufficient in prompting the next nerve cell to fire: no (EPSP) activation**
- Rather than initiating this system of action, NE acts on its A1 receptor as a **neuromodulator** on the target cell (which receives major excitatory input concurrently), thereby **amplifying some other major transmitter function** which is already going on

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Serotonin Action

- **Mescaline:** indirect agonistic action; increased affinity
- **5-HT2a stimulation promotes glutamate release** indicated by increase in EPSPs in the cerebral cortex: causing cognitive, perceptual, and affective distortions produced by hallucinations
- **Selectivity for 5-HT2 receptor 6**
- **Activation of 5-HT2a receptors causes a transient increase in intracellular Ca+2**
- **K+ conductance may also be affected**

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Dopamine Action

- Mild stimulant and reinforcer
- Mescaline: mixed/ indirect agonist action
- Greater implication in LSD action

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Glutamate

- Mescaline (via 5HT2a receptors) enhances glutamatergic transmission
- Alternative schizophrenia models based upon psychotomimetic properties of antagonists of the NMDA subtype of the glutamate receptor suggest that the effects of NMDA antagonists not only involve 5HT2a but may also be mediated through excess activity at non-NMDA (i.e. AMPA/kainate) glutamate receptors

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Norandrenergic Effects

- **Norandrenergic effects** include input from the LC projects to layer V pyramidal cells in the neocortex (as do 5HT inputs from raphe nuclei)
- **Noradrenaline** acting via alpha –1 receptors also induces an increase in glutamate release

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LSD/ Mescaline Juxtaposition

- Highlight the complexities of pharmacological research of hallucinogens and gaps in our current understanding
- Understanding the scope, structure, functioning, and differentiation between various psychoactive sites
- Taken from Austin, J.H. (1998)

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LSD/ Mescaline Juxtaposition..

- Hallucinogens share action on second messenger systems; however, not all psychoactive drugs act in and on the same receptor mechanisms
- For example, LSD does stimulate the enzyme which makes cyclicAMP, but mescaline and psilocine do not
- LSD has additional properties as a dopamine agonist, neither psilocine nor mescaline acts as a direct DA agonist
- However, mescaline does release some DA from DA nerve terminals and indirectly suppresses the firing of ST nerve cells, without acting directly on them

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LSD/ Mescaline Juxtaposition.. Alternate Mechanisms of Action?

- LSD stops the firing of ST nerve cells in the raphe nuclei: hypothesized mechanism of action (hallucination)
- However, general inhibition of ST cells of the raphe nuclei shows no direct relationship with LSD-induced behaviors
- Tolerance to LSD results quickly in humans, no longer producing psychic changes after the fourth daily dose

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LSD/ Mescaline Juxtaposition.. Sites of Action?

- Mescaline, too, causes hallucinations, but when applied locally in the RN does not inhibit ST cell firing
- Other compounds (lisuride) do block the firing of cells in the dorsal RN but do not cause hallucinations
- LSD also enhances the actions of NE indirectly

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LSD/ Mescaline Juxtaposition..

- Microinjection of LSD or mescaline into the locus ceruleus results in the inhibition of background firing of NE cells
- Ultimately results in increased NE cell sensitivity to peripheral stimulation thought to result from an increase in signal-to-noise ratio

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LSD/ Mescaline Juxtaposition… Hyperfrontality Examined?

- LSD and mescaline activate ST2 receptors on the post-synaptic element far distant from the neurons in the locus ceruleus
- Evidence suggests that these ST2 receptors on distant cells play a crucial role in producing hallucinations caused by various psychedelic drugs
- ST cells of the dorsal RN are thought to target higher cells of the frontal cortex which are rich in ST2 receptors. But the process does not stop here…

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LSD/ Mescaline Juxtaposition..

- Another set of impulses return from such far distant postsynaptic target cells travel back down to the brain stem to again make NE cells fire faster in response to stimuli arriving from the outside
- Several avenues exist through which an *initial activation of ST2 receptors can translate, indirectly, to an increased release of NE*

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LSD/ Mescaline Juxtaposition.. Possible Regional Structures?

- In primates, dense networks of NE terminals envelop most sensory pathways, so whichever ST mechanism causes more NE to be released can soon go on to influence perceptual functions throughout many vital regions
- Increased release of NE in regions such as the pulvinar, lateral posterior thalamic nuclear group, caudal parietal cortex, superior colliculus, and the reticular nucleus of the thalamus could contribute to the remarkable sensate phenomena caused by LSD or mescaline

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LSD/ Mescaline Juxtaposition..

- So what is actually occurring??
- Largely uncertain specific action

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Plausible Mechanisms of Drug Action: Hallucinations

- Elaborate mixture of interactions at sites both presynaptic and postsynaptic among ST, NE, and DA nerve cell systems
- Dynamic mixture modulates chiefly the excitatory properties expressed by the other major transmitter systems
- Secondary metabolic processes cascade, carrying potential to modify mental functions, especially space/time perception
- Psychophysiological ordeal triggers emergency responses commiserating in a variety of sensations/ perceptions triggered through ancient circuitries.

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Salvia divinorum

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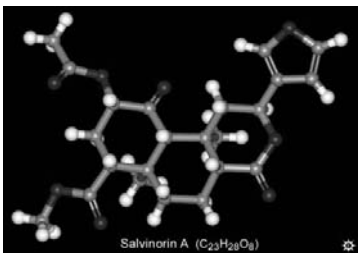
Salvia divinorum: Salvinorin A



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Salvia

- Soft-leaved green plant native to Mexico: Labiatae: Mint Family
- Psychoactive chemical: **Salvinorin A & B**

  Presents "significant research and therapeutic potential in fields such as psychopharmacology, psychiatry, and complementary disciplines such as herbal medicine… research may pinpoint unique antidepressant action" (Hanes 2001).

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Salvia…

- Traditionally employed by Mazatec Indians in medico-magical divination ceremonies: numerous demonstrated therapeutic applications
- E.g.- Administered for diarrhea, headache, rheumatism, and anemia

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Salvia…

- **Low potential for abuse**: No CSA Schedule status thus far: no "substantial similarity" to other illicit molecular compounds
- **Salvinorin A's chemical structure entirely unique among psychoactive molecules**: diterpenoid agent devoid of nitrogen
- Precise neurotransmitter receptor with affinity for salvinorin A discovered in August of 2002: **Kappa Opioid receptors**
- Psychoactive effects are **inconsistent and evanescent: individual differences/ sensitivity**

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Salvia's Psychic Effects

- **Dissociative state**: out-of-body experience
- **Geometric shapes** in vision
- **Hallucinations**: vivid imagery, encounters with beings, travel to other places, planets or times, living years as the paint on a wall or experiencing the full life of another individual

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Salvia's Psychic Effects…

- **POSITIVE**
- short duration (when smoked)
- radical perspective shifting
- increase in sensual and aesthetic appreciation
- creative dreamlike experience
- insight into personal issues

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Salvia's Psychic Effects…

- **NEUTRAL**
- powerful open and closed eye visuals
- general change in consciousness
- altered perceptions
- change in body temperature (?)
- sensation of physical push, pressure, or wind
- sensation of entering or perceiving other dimensions, alternate realities
- feeling of 'presence' or entity contact
- dissociation at high doses, walking or standing

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Salvia's Psychic Effects…

- **NEGATIVE**
- overly-intense experiences
- fear, terror and panic
- increased perspiration
- possible difficulty integrating experiences

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Salvia…Pharmacokinetics

- **Ingested orally**: chewed leaves: juice held in mouth: intense bitterness: slower onset
- **Smoked**: extracts 5x, 6x, and 10x concentration most efficient
- **Single inhalation** of concentrated extract may produce transient effects
- **Steep "learning curve":** psychoactive effects associated with large doses aversive
- **No cases of dependency**: few repeat experience

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Salvia…Pharmacokinetics

- **Dosages**: Leaf Potency: smoked
  Light: .25g; Common: .5g; Strong: .75g

Dosages: 5x extract: smoked
Light: 1/20 – 1/10g
Common: 1/15 – 1/10g
Strong: 1/10 – 1/4g

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Salvia…Pharmacokinetics

- **Smoked Salvia divinorum**:
- **Onset**: 20-60 seconds
- **Coming Up**: 1-2 minutes
- **Plateau**: 5-10 minutes
- **Coming Down**: 20-30 minutes
- **After Effects**: 15-20 minutes

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Salvia Pharmacodynamics

- **No cases of psychotic deterioration or other medical compilations**: lack any known toxicity, gastrointestinal, or cardiovascular impairment.
- **Danger: anxiety reactions**: usually limited due to brief duration of effects
  - Extraneous noise/ opening eyes may terminate the psychoactive effects.

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Salvia Pharmacodynamics…

- Salvinorin A is a potent kappa-opioid receptor agonist
- KOR previously known for its ability to cause strange psychoactive effects not expected from the opioid system:
  - Mediate psychotomimetic effects
- Salvinorin A's effects are entirely unique and thought to act independently of 5HT2a systems, which most visionary drugs act on

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Salvia Pharmacodynamics…

- Research suggests the possibility of specific kappa-opioid antagonists acting as anti-psychotics: may represent a novel class of psychotherapeutic compounds
- Suggested that KORydynorpin peptide system functions to modulate human perception
- Future research on whether naltrexone (general opioid antagonist) might eliminate/reduce effects of Salvinorin A
- Also whether other KOR antagonists such as enadoline cause effects similar to Salvinorin

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Salvia Conclusions

- "Education aimed at raising awareness of the plant's unpredictable and occasionally upsetting psychoactive effects, rather than criminal prohibition, is the key to reducing individual and social harm with respect to S. divinorum and its active principle" Executive Summary (2003)

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