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Salvia divinorum and Salvinorin A: new pharmacologic findings

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Abstract

The diterpene salvinorin A from *Salvia divinorum* (Epling and Jativa-M), in doses of 200–500 μg produces effects which are subjectively identical to those experienced when the whole herb is ingested. Salvinorin A is effectively deactivated by the gastrointestinal system, so alternative routes of absorption must be used to maintain its activity. Traditionally the herb is consumed either by chewing the fresh leaves or by drinking the juices of freshly crushed leaves. The effects of the herb when consumed this way depend on absorption of salvinorin A through the oral mucosa before the herb is swallowed.

Keywords: *Salvia divinorum*; Salvinorin A; Psychoactive plants; Psychoactive compounds

1. Introduction

Salvia divinorum is used by the Mazatec Indians of northeastern Oaxaca, Mexico primarily for its psychoactive effects which aid in ritual divination (Wasson, 1962, 1963). It is also employed remedially to treat various health conditions (Valdes et al., 1983).

The first live specimens of *S. divinorum* were given to Carl Epling by R. Gordon Wasson in 1962 and were cultivated at the University of California in Los Angeles (Wasson, 1962). Cuttings of this original clone were distributed to other botanical collections over the years and most of the plants in cultivation in the USA today originated from this original clone (Valdes et al., 1987). Recently, other clones have been appearing in collections. As of this writing there are at least four different clones present in public and private botanical collections in the USA.

The chemistry of this plant has been investigated several times. The diterpenes salvinorin A and salvinorin B have been identified and characterized. Salvinorin A has been shown to be active in mice while salvinorin B was inactive. No human studies with these compounds have previously been reported (Ortega et al., 1982; Valdes et al., 1984). Trace amounts of other diterpenes have been detected but have not yet been characterized (Valdes et al., 1984).

There are two methods of ingestion traditionally employed: either the fresh whole leaves are masticated and swallowed or, alternatively, the leaves are crushed to extract the juices which are

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then drunk. Of these two methods, chewing of the leaves is most reliable and requires a smaller quantity of leaves. The liquid preparation is often ineffective and when it does produce effects they are usually much milder than those reported for chewing, even when substantially larger quantities of leaves are used in the preparation.

When the leaves are chewed whole they must first be chewed well enough to be easily swallowed and so spend quite some time in contact with the oral mucosa. When the leaf juice preparation is consumed it can be swallowed fairly quickly and consequently spends relatively little time in contact with the oral mucosa. The level of effects reported relates quite closely to the length of time the material spends in the mouth before being swallowed.

This presentation describes the effects of salvinorin A in humans, its deactivation by the gastrointestinal system and the essential role of the oral mucosa as an absorption site for salvinorin A from orally ingested leaves.

2. Materials and methods

All plant material used in this study was propagated from the clone originally brought into the USA by R. Gordon Wasson in 1962.

2.1. Salvia divinorum leaves

In order to investigate the relative importance of the oral mucosa as an absorption site for the active principals in *S. divinorum* leaves, the following experiments were carried out by six volunteers using ten large fresh leaves each (approximately 30 g total) which had been homogenized with 100 ml water using a blender. Each experiment was separated by several days.

(A) The material was swallowed as quickly as possible with the intention of quickly bypassing the oral mucosa; then the mouth was immediately rinsed with water to wash away any residual material that might be clinging to the oral mucosa. None of the volunteers reported any noticeable effects when the material was ingested in this manner.

(B) The material was held in the mouth for 10 min without swallowing; then the entire contents were spit out. This method proved consistently effective with all of the volunteers reporting very definite psychoactive effects.

2.2. Salvinorin A

Salvinorin A was isolated following the method of Valdes (Valdes et al., 1984). The identity of this material was verified by comparison with an authentic sample of salvinorin A using TLC, melting point and NMR.

Salvinorin A has previously been shown to be active in mice but it has remained uncertain whether this compound is responsible for the psychoactive effects produced in humans. In order to determine this, salvinorin A was administered to a group of 20 volunteers.

When salvinorin A was encapsulated and swallowed in doses as high as 10 mg there was no detectable activity. Experiments with the leaves indicate that the active principle of the plant is deactivated by the gastrointestinal system. To test for activity of salvinorin A, alternative routes of ingestion were attempted. Salvinorin A is not water soluble so injection was not attempted.

Absorption through the oral mucosa. A 2-mg quantity of salvinorin A was dissolved in 1 ml anhydrous ethyl alcohol then sprayed on the inner surfaces of the mouth using an aspirator. The material proved to be active; however only a small percentage is absorbed this way before it gets dispersed by salivary flow. Consequently this method was inefficient and results were inconsistent.

Inhalation of the vaporized compound. The material was placed on a piece of aluminum foil. A butane micro torch was then held beneath the foil until the material was seen to vaporize. As soon as this began, the vapors were inhaled through a 15-mm glass tube.

Inhalation of the vapors produced by heating salvinorin A proved to be the most efficient method of ingestion tested. When 200–500 μg of salvinorin A is vaporized and inhaled the subjective effects produced are identical to those typically produced by the fresh herb. Doses up to 2.6 mg were tested in this manner. Typically threshold effects are noted at about 200 μg.

2.3. Effects

When salvinorin A is absorbed through the oral

mucosa the first effects are usually experienced in 5–10 min. The strength of the effects builds very quickly over a few minutes, maintaining a plateau for about 1 h. The effects gradually subside over another 1-h period. The evolution of effects over time is identical to that of orally ingested *S. divinorum* leaves.

When salvinorin A is vaporized and inhaled the full effects are experienced in about 30 s. There is almost no transition period experienced. The strongest effects last 5–10 min and then gradually subside over about 20–30 min. As dosage increases above 1 mg the duration of the effects are somewhat increased. A similar evolution of effects is reported for smoked *S. divinorum* leaves.

The oral mucosa apparently acts as a time release buffer, slowly diffusing salvinorin A into the blood stream; hence when consumed orally, the effects begin more gradually, last longer and subside over a longer period of time than when the material is vaporized and inhaled. Although variable in duration, the effects experienced have the same overall characteristics regardless of the route of absorption used.

The nature of the effects experienced depends on many factors including dose, set and setting. Frequently people report having seen visions of people, objects, and places. With doses above 1 mg, out of body experiences are frequent. Occasionally individuals get up and move about with no apparent awareness of their movements or behavior. Some individuals speak gibberish during the most intense phase of the experience, others laugh hysterically.

Certain themes are common to many of the visions and sensations described. The following is a listing of some of the more common themes:

(1) Becoming objects (yellow plaid French fries, fresh paint, a drawer, a pant leg, a Ferris wheel, etc.).
(2) Visions of various two dimensional surfaces, films and membranes.
(3) Revisiting places from the past, especially childhood.
(4) Loss of the body and/or identity.
(5) Various sensations of motion, or being pulled or twisted by forces of some kind.
(6) Uncontrollable hysterical laughter.
(7) Overlapping realities. The perception that one is in several locations at once.

Some of the effects appear to parallel those of other hallucinogens (i.e. the depersonalization experienced with ketamine, the rapid onset of effects and short duration of smoked DMT). The volunteers who were experienced with other hallucinogens all agreed that despite some similarities, the content of the visions and the overall character of the experience is quite unique.

2.4. Receptor Site Screening and MAO Inhibition

A sample of salvinorin A was submitted to NovaScreen™ for receptor site screening. At screening concentrations of 10^{-5} M there was no significant inhibition (i.e. 50% or less) for the following sites.

Neurotransmitters: Adenosine, alpha 1, alpha 2, beta, dopamine 1, dopamine 2, $GABA_A$, $GABA_B$, serotonin 1, serotonin 2, muscarinic 3, NMDA, kainate, quisqualate, glycine (stry sens.).

Regulatory sites: Benzodiazepine(centrl), glycine (stry insens.), PCP, MK-801.

Brain/gut peptides: angiotensin Ty2, arg-vasopressin V1, bombesin, CCK central, CCK peripheral, substance P, substance K, NPY, neurotensin, somatostatin, VIP.

Growth factors and peptides: ANF1, EGF, NGF.

Ion channels: Calcium (type N), calcium (type T and L), chloride, potassium (low conduct).

Second messengers: Forskolin, phorbol ester, inositol triphosphate.

Monoamine oxidase inhibition: Monoamine oxidase A, monoamine oxidase B.

3. Discussion and conclusions

When *S. divinorum* leaves are consumed, either by chewing the fresh leaves or by retaining the leaf juices in the mouth, enough of the highly active compound salvinorin A is absorbed through the oral mucosa and into the blood stream to produce a psychoactive effect. Swallowing of the herb is unnecessary and its effects are increased by lengthening the amount of time that the herb remains in the mouth. When the leaf juices are quickly swallowed, minimizing contact with the oral mucosa, the only route of absorption is

through the gastrointestinal system where salvinorin A is deactivated before entering the blood stream. When pure salvinorin A is encapsulated and swallowed it is inactive even at relatively large doses, but when absorbed through the oral mucosa or vaporized and inhaled is extremely active. It is likely that if salvinorin A were administered by injection, it would prove to be active at even lower doses than those described in this paper.

Salvinorin A is the first entheogenic diterpene reported and is active in humans at extraordinarily low doses. It does not appear to affect any of the receptor sites affected by other hallucinogens. Further research into the methods of action and possible medicinal values of this and similar compounds may prove to be quite rewarding.

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