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Dark Classics in Chemical Neuroscience: Mescaline

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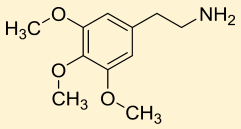
ABSTRACT: Archeological studies in the United States, Mexico, and Peru suggest that mescaline, as a cactus constituent, has been used for more than 6000 years. Although it is a widespread cactus alkaloid, it is present in high concentrations in few species, notably the North American peyote (*Lophophora williamsii*) and the South American wachuma (*Trichocereus pachanoi*, *T. peruvianus*, and *T. bridgesii*). Spanish 16th century chroniclers considered these cacti "diabolic", leading to their prohibition, but their use persisted to our days and has been spreading for the last 150 years. In the late 1800s, peyote attracted scientific attention; mescaline was isolated, and its role in the psychedelic effects of peyote tops or "mescal buttons" was demonstrated. Its structure was established by synthesis in 1929, and alternative routes were developed, providing larger amounts for pharmacological and biosynthetic research. Although its effects are attributed mainly to its action as a 5-HT_{2A} serotonin receptor agonist, mescaline binds in a similar concentration range to 5-HT_{1A} and α_{2A} receptors. It is largely excreted unchanged in human urine, and its metabolic products are apparently unrelated to its psychedelic properties. Its low potency is probably responsible for its relative neglect by recreational substance users, as the successful search for structure−activity relationships in the hallucinogen field focused largely on finding more potent analogues. Renewed interest in the possible therapeutic applications of psychedelic drugs may hopefully lead to novel insights regarding the commonalities and differences between the actions of individual classic hallucinogens.



KEYWORDS: *Mescaline, hallucinogen, peyote, wachuma San Pedro, synthesis, biosynthesis, metabolism, pharmacology, structure−activity relationships*

INTRODUCTION, HISTORY, AND OCCURRENCE

Mescaline is exceptional among the classic hallucinogens because of its outstandingly long record of use. Thus, dried tops or "buttons" of the peyote cactus *Lophophora williamsii* (Lem.) Coulter, the preferred form of ingestion in North America, have been found in an archeological site in southwestern Texas and ^{14}C-dated to about 5800−6000 years before present (YBP).[1−3] More ancient still is a spine cluster of the psychedelic cactus *Trichocereus peruvianus* Britton & Rose, found associated with artifacts and other remains dated to 6200−6800 YBP in a cave in northern Peru.[4] In the same general region the more widely used wachuma *T. pachanoi*, better known as San Pedro, is depicted on steles and ceramic vessels of the Cupisnique-Chavín cultures from at least 2500 YBP.[5] The purpose of peyote and wachuma use by these ancient cultures can only be guessed, but it is reasonable to assume that these cacti were recognized as psychedelic and employed as such.

Current use of pure mescaline, either isolated from natural sources or synthesized in the laboratory, seems to be infrequent, possibly due to the relatively high doses required to attain a full psychedelic experience. By contrast, the ingestion of peyote buttons or wachuma (San Pedro) brews is common in some cultures and subcultures and seems to be growing in geographic range and popularity. Thus, while ceremonial peyote use was widespread in the Aztec empire and northern Mexico at the time of the Spanish conquest,[6] religious persecution confined it to areas near the Pacific coast and up to southwest Texas, only to spread north starting around 1880 with "a new kind of peyote ceremony" inaugurated by the Kiowa and Comanche people. This religion, incorporated legally in the United States in 1920 as the Native American Church, has since reached at least as far as Saskatchewan, Canada.[7] Similarly, wachuma was represented on artifacts of different pre-Inca cultures almost all down the coast of present-day Peru, but after the Spanish invasion, its use became restricted to *curanderos* (healers) in the north of that country.[8] However, from the mid-20th century, it spread to southern Peru, Bolivia, and Chile for both psychotherapeutic and recreational purposes. Due to its ornamental value, its ease of cultivation, and rapid growth, *T. pachanoi* is now fairly commonplace from Ecuador to central Chile and available in trade as a house or garden plant at least in the United States and Europe.

Scientific interest in peyote exploded in the second half of the 19th century, after the publication of press reports such as one in the California Democrat (February 9, 1894) describing the use of a cactus as an intoxicant by the Kiowa and other Native American tribes. Its nonreligious, nonceremonial use may be older, as the ethnographer Carl Lumholtz wrote that during the United States Civil War, Texas Rangers soaked peyote in water and drank the intoxicating liquid.[9]

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Toward 1888, Louis Lewin, a German toxicologist visiting the United States, received a sample of a cactus from Mexico ("whose place of origin is kept secret" but "is called Muscale buttons and is sold and used as a narcotic stimulant" or more literally (*Genussmittel* in German) "something to enjoy").[10] He submitted it to Paul Hennings of the Berlin Botanical Museum, who considered it a new *Anhalonium* species and named it *A. lewinii*. Lewin obtained a crude alkaloid extract of the cactus which he called "Anhalonin" which later proved to be different from mescaline.[10] Arthur Heffter published a paper in 1894 in which he mentioned letters from a Dr. Tischer describing the use of "pellote" as an intoxicant and as medicine in northern Mexico. Heffter isolated pellotine (Figure 1) from this

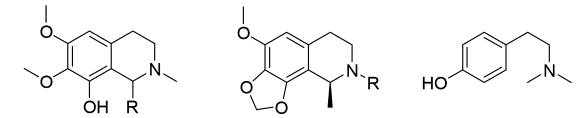

Figure 1. Nonmescaline peyote alkaloids.

material,[11] and two years later isolated mescaline for the first time.[12] In 1898 he tested both alkaloids in humans, recommended pellotine as a sleep inducer, and most significantly showed that mescaline was responsible for the remarkable effects of peyote buttons.[13]

Although the presence of mescaline in wachuma had been suspected for years, the first report of its isolation from the cactus (misidentified as *Opuntia cylindrica*) was merely as "a yellowish liquid, sparingly soluble in water, forming a water-soluble hydrochloride".[14] This, administered to humans, mimicked the effect of the cactus extract.[15] However, its definitive identification as mescaline was only confirmed in 1960 in two different laboratories.[16,17]

Mescaline has been documented in many species aside from *Lophophora williamsii* (the actual peyote) and *T. pachanoi* (wachuma, San Pedro, San Pedro hembra). Nevertheless, this alkaloid is seldom abundant and, because of its low psychedelic potency (oral doses of about 300 mg of the free base are required for a full-blown hallucinogenic experience), *L. williamsii* and *T. pachanoi* are the only widely consumed botanical sources. *T. peruvianus* (Peruvian torch, San Pedro macho) and *T. bridgesii* (Bolivian torch), both also called wachuma, are used, though less frequently. An exhaustive list of mescaline-containing cacti and their chemistry was compiled by Trout.[18]

Regarding the nomenclature of these cacti, the genus *Lophophora* was only segregated from *Anhalonium* by Coulter in 1894, explaining why peyote was called *Anhalonium williamsii* or *A. lewinii* in the early literature. The homeopathic pharmacopoeia still retains the older name. Today, there are only two generally recognized *Lophophora* species, *L. williamsii* and *L. diffusa* (Querétaro peyote). The latter contains little mescaline, and the tetrahydroisoquinoline pellotine is the main alkaloid. This may have been the material first analyzed by Heffter. His "pellote" paper includes two beautiful illustrations by R. Sperling of *Anhalonium williamsii* and *Anhalonium lewinii*.[11] Studying a sample of plants found in commerce in Japan and probably not representative of wild populations, it was suggested that there are two different forms of *L. williamsii*, one of them lacking mescaline, that can be distinguished from each other and from *L. diffusa* morphologically, on the basis of their mescaline content and by the length of a chloroplast DNA sequence.[19]

Trichocereus is a South American genus comprising about 45 species. It has been proposed that *Trichocereus* be included in the related *Echinopsis*, but this change is not supported by DNA analysis.[20,21] As a consequence, *T. pachanoi* sometimes appears in the literature as *E. pachanoi*, *T. peruvianus* as *E. peruviana* and, more confusingly, *T. bridgesii* as *E. lageniformis*. Moreover, *T. pachanoi* and *T. peruvianus* have recently been combined into a single species as *T. macrogonus var. pachanoi* and *T. macrogonus var. peruvianus*.[22] In this review, we retained the traditional name *Trichocereus*.

As early as 1898, Heffter remarked that the upper chlorophyll containing part of what he called *Anhalonium williamsii* is very bitter, while the roots are hardly bitter at all. An analysis carried out on cacti received "fresh from Saltillo" showed that the green tops contained 6−7 times higher concentrations of total alkaloids than the rest of the plant.[13] Klein et al. reported that 10 individual peyote plants from a southern Texan population contained (calculated on dry weight) 1.82−5.5% mescaline in the crown and 1−2 orders of magnitude less in the nonchlorophyllous stem and root, lending modern support to Heffter's work and the traditional use of the tops.[23] Nevertheless, a recent paper reported the analysis of the crown and the root of a single *L. williamsii* plant which gave similar total alkaloid contents in both parts but with radically different compositions. Practically all the mescaline (15.7% of the alkaloids) was found in the crown with the simple isoquinolines anhalidine, pellotine, lophophorine, and anhalonine making up most of the rest (14.6, 19.8, 13.3 and 6.0%, respectively), and very little of these in the "root", where the phenethylamine hordenine was by far the major alkaloidal component.[24]

Considering that these "companion" alkaloids may play a significant role in the absorption, distribution, metabolism, and excretion of mescaline, more complete analyses of peyote samples would be most welcome. Peyote plants from Chihuahuan desert and Tamaulipan thornscrub populations in Texas were analyzed for mescaline content. The average concentrations varied within a fairly narrow range (2.77−3.52%) and did not differ significantly by location.[25]

A study of interindividual variation in *T. pachanoi* was published in 2010. Identical processing of dried subepidermal green tissue from five different specimens gave results ranging from 0.54 to 4.7% mescaline, evidencing the high variability of this species. A single *T. peruvianus* specimen gave 0.24% of mescaline, and the more mescaline-rich of two *T. bridgesii* samples contained 0.47%, apparently contradicting some popular reports that these cacti are more potent than *T. pachanoi*.[26] Only the green tissue was analyzed, which is generally used to prepare wachuma extracts and is reasonable in view of analytical results with peyote and is also suggested for the more closely related *T. terscheckii*, which contains less mescaline than its *N*,*N*-dimethyl derivative trichocereine.[27] Nevertheless, more thorough analyses are necessary to better characterize mescaline-rich accessions and determine the distribution of mescaline and mescaline precursors[28] at different distances from the axis and from the tip of this cactus, which grows more than 5 m tall. In summary, much work is still needed to address variations in mescaline content within species and within individual cacti with reference to provenance, soil, season, and even hour of sampling.

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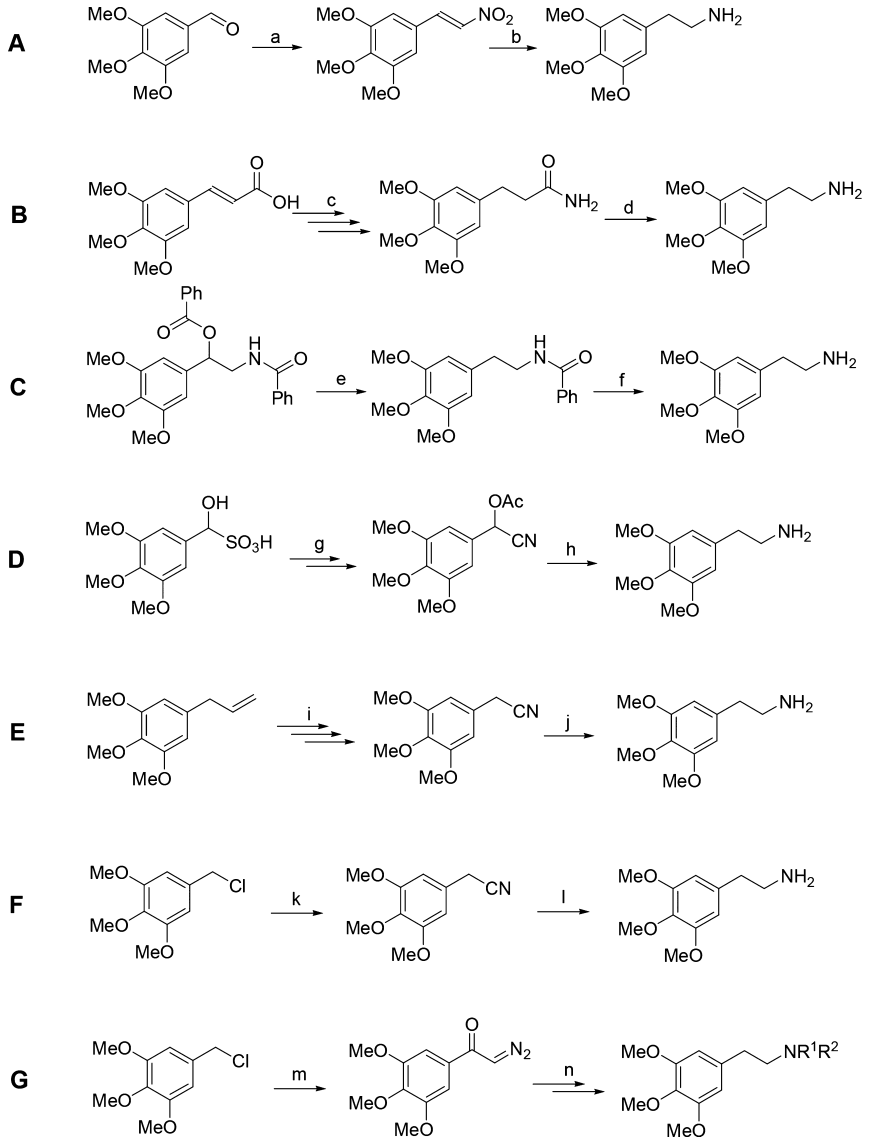
Scheme 1. Classic Mescaline Syntheses[a]



[a]A: (a) $MeNO_2$, base; (b) Zn-AcOH; then Na/Hg-AcOH; or cathodic reduction in EtOH-HCl; or preferably $LiAlH_4$; B: (c) Na/Hg-EtOH-AcOH; then $SOCl_2$, then NH_3; (d) NaOBr; C: (e) tetralin-Pd; (f) 20% KOH; D: (g) KCN; then Ac_2O; (h) H_2−Pd; E: (i) O_3; then H_2−Pd; then $HONH_2$; then Ac_2O: (j) H_2−Pd; F: (k) KCN; (l) $LiAlH_4$: G: (m) CH_2N_2; (n) $AgNO_3/NHR^1R^2$; then $LiAlH_4$.

CHEMISTRY, SYNTHESIS, AND BIOSYNTHESIS

Heffter began his study of mescaline by preparing and analyzing salts, including the neutral sulfate dihydrate $(C_{11}H_{17}NO_3)_2 \cdot H_2SO_4 \cdot 2H_2O$. Surprisingly, he reported the free base as a solid softening above 100 °C and melting around 150−160 °C, which was not analyzed. As all subsequent work describes this alkaloid as a liquid at room temperature or as a solid melting at 35−36 °C, it seems likely that the solid mentioned was in fact a carbonate, as mescaline is known to readily absorb CO_2 and water from the atmosphere. Aside from its correct overall formula $C_{11}H_{17}NO_3$, Heffter showed the presence of three methoxy groups by Zeisel analysis,[12] and permanganate oxidation to the known trimethylgallic acid proved the ring substitution pattern.[29] He suggested that mescaline might be *N*-methyl-3,4,5-trimethoxybenzylamine but discarded this hypothesis a few years later by synthesizing the latter compound.[30] More than two decades elapsed until the correct structure was finally demonstrated by synthesis from 3,4,5-trimethoxybenzaldehyde via the nitrostyrene obtained by base-catalyzed condensation with nitromethane and subsequent reduction in two steps to 3,4,5-trimethoxyphenethylamine (Scheme 1A).[31]

As part of a pioneering study of the structure−activity relationships of mescaline, which required the synthesis of isomers and of mono- and dimethoxyphenethylamines, an improved method (Scheme 1B) was developed by Slotta and Heller via appropriately substituted hydrocinnamic acids, their two-step conversion into amides, and a final Hofmann degradation.[32] Kindler and Peschke prepared *N*-benzoyl-*β*-benzoyloxymescaline from 3,4,5-trimethoxybenzaldehyde and later used it to obtain *N*-benzoylmescaline in an early example of transfer hydrogenation by heating the benzoyloxy compound in tetralin with finely divided palladium, followed by basic hydrolysis to afford mescaline (Scheme 1C).[33] Unsatisfied with this method, the same authors developed another one which they considered much more practical and efficient via the bisulfite adduct of the aldehyde, substitution of the sulfite

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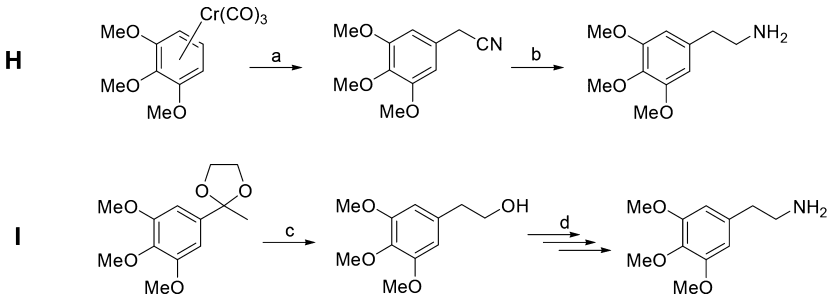
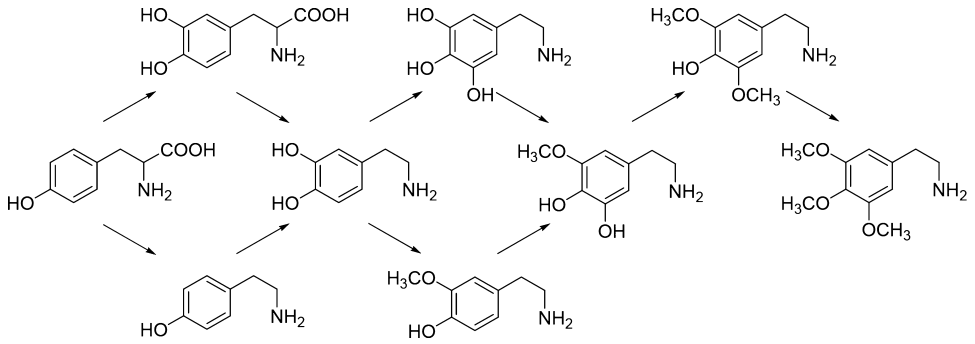
Scheme 2. Modern Mescaline Syntheses[a]



[a]H: (a) $LiCH_2CN$; (b) $LiAlH_4$. I: (c) 9-BBN; then H_2O_2; (d) MsCl; than NaN_3; then $LiAlH_4$.

Scheme 3. Biosynthesis of Mescaline (According to Ref 45)



moiety by cyanide, acetylation of the hydroxyl group, and catalytic hydrogenation in a strongly acidic medium (Scheme 1D).[34] Slotta subsequently improved his synthesis, reducing the precursor nitrostyrene electrolytically in one step and in excellent yield (Scheme 1A).[35] The next year, elemicin was converted in three steps to 3,4,5-trimethoxyphenylacetonitrile which was then reduced to mescaline (Scheme 1E).[36]

In 1950 Erne and Ramírez were the first to use lithium aluminum hydride (LAH) to reduce 3,4,5-trimethoxy-β-nitrostyrene.[37] The next year, apparently unaware of this work, Benington and Morin performed the same synthesis,[38] and shortly thereafter a note was published recapitulating the seemingly obvious benzyl alcohol−chloride−nitrile−amine route that had been discarded as inefficient in the 1930s, now using LAH reduction, but less satisfactorily.[39] This methodology was used by Dornow and Petsch,[40] with K[^{14}C]CN, to prepare radioactive mescaline for an early pharmacokinetic study (Scheme 1F).[41] LAH was also employed to obtain mescaline by reduction of 3,4,5-trimethoxyacetamide, prepared in turn from the 3,4,5-trimethoxybenzoyl chloride via the diazoketone. This method, in spite of its relatively poor overall yield, was used to prepare *N*-methylmescaline and *N*,*N*-dimethylmescaline (trichocereine) (Scheme 1G).[42]

Mescaline has also been synthesized, preparing the precursor 3,4,5-trimethoxyacetonitrile by reacting (η^6-1,2,3-trimethoxybenzene)chromium tricarbonyl (from1,2,3-trimethoxybenzene and chromium hexacarbonyl) with acetonitrilyllithium (Scheme 2, H).[43] A novel and unexpected acetophenone ketal ring opening by 9-borabicyclo[3.3.1]nonane with a 1−2 oxygen migration, applied to 2-methyl-2-(3,4,5-trimethoxyphenyl)-1,3-dioxolane, led to mescaline in 47% overall yield (Scheme 2, I).[44]

The biosynthesis of mescaline in *L. williamsii* and *T. pachanoi* was studied in the late 1960s by feeding ^{14}C-labeled putative precursors to the plants, starting with tyrosine. The general and still accepted scheme is that put forth by Lundström and Agurell (Scheme 3).[45]

At that time, there was little interest or technical expertise to study the enzymes involved or the relative importance of alternative pathways. Nowadays, we would pose questions about the derailing of 4-hydroxyphenethylamine to the synthesis of hordenine and candicine, or of 3,4-dihydroxy-5-methoxyphenethylamine to the simple isoquinolines of the cactaceae, as well as the mono- and di-*N*-methylation of mescaline. With appropriate knowledge, we could consider metabolic engineering approaches to optimize or suppress the biosynthesis of mescaline or other alkaloids in cacti. Biosynthetic thinking and practice have evolved considerably over this half century, and a recent study has identified candidate genes for tyrosine/DOPA decarboxylase, hydroxylases, and *O*-methyltransferases in *L. williamsii* tissues.[24] This work will foreseeably serve as the basis for more detailed studies on the formation of mescaline and related cactus alkaloids.

PHARMACOLOGY AND STRUCTURE−ACTIVITY RELATIONSHIPS

Although peyote contains at least 15 different phenethylamine and isoquinoline alkaloids that may all be bioactive,[46] the psychedelic properties of this cactus are attributed to mescaline.[47] Stimulated by its remarkable history as a psychedelic compound, the systematic pharmacological characterization of mescaline began more than a century ago and developed rapidly during the first decades with descriptions not only of its effects in humans and experimental animals but also exploring possible clinical applications in the study of psychosis and the treatment of schizophrenia.[48] Nevertheless, the possibility of using mescaline as a therapeutic agent kindled a still unsolved controversy. The discussion has been reintroduced recently thanks to evidence from studies in humans that

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provides renewed support for the therapeutic potential of psychedelics.[49−52] Additionally, advances in the knowledge of how drugs such as mescaline or LSD may alter synapse-related gene expression affecting neuronal connectivity in key brain regions have renewed interest in exploring possible uses of psychedelics in biomedicine.[53]

Lewin's original "Anhalonin" was a potent "reflex tetanus-producing" poison resembling strychnine in several species with no indication of any psychotropic activity.[10] Heffter isolated anhaline (now identified with hordenine) from *Anhalonium fissuratum*, and pellotine from *A. williamsii* and studied their pharmacology in two frog species, where they exerted actions resembling those of Lewin's "Anhalonin". He also tested both alkaloids in humans, including himself, observing only drowsiness and, apparently, some slowing of the pulse.[11] Shortly after Heffter's first 1894 publication, Lewin noted that the "tetanizing" effect, which he was able to confirm with crystallized (presumably pure) anhalonine and its hydrochloride, was unrelated to the reported effects of mescal buttons in humans.[54] Heffter then examined a fresh sample of *A. lewinii* which gave two crystalline sulfates A and B in amounts too small to allow any chemical characterization with the methodologies then available, but they were tested in frogs with the result that A was weakly active while B was clearly toxic. He concluded, after isolating much more mescaline, that this was the same as his A.[12] He summarized and extended the pharmacological studies in live animals on the five *Lophophora* alkaloids isolated until then, confirming the narcotic effect of mescaline in frogs and its lack of obvious toxicity in mammals.[13]

However, a remarkable result was noted with a dog that received 200 mg subcutaneously. About an hour after administration he began to whine and bark, not at the observer but toward the opposite side of his cage. When called he turned around and wagged his tail and then returned to his barking at the back of the cage, a peculiar behavior that lasted "for a long while". Remarkably, this work was complemented by studies in Heffter himself, showing that mescaline is the psychedelic constituent of peyote. After experiencing the effect of mescal buttons, he tried 1.0 g of crude alkaloid sulfates extracted from a similar amount of cactus. In this experiment he noticed the visual changes barely an hour after swallowing the drug, and these lasted "extraordinarily long", with minor manifestations lasting into the next morning. Heffter was convinced that mescaline was responsible for these effects after taking 0.15 g of the hydrochloride which, however, took slightly more than 2 h to produce visuals and noticeably weaker effects than in his previous experiments, which he suggested might be due either to a very low dose or to the absence of other alkaloids which might modulate the effects of pure mescaline.[13]

Prentiss and Morgan were the first to perform medical observations with peyote.[55] They noted that "mescal buttons possess properties which are remarkable, the exact likeness of which is not found in any other known drug, and also that it possesses virtues which, when applied in the treatment of certain diseased conditions, may prove the drug a valuable addition to our present list of therapeutic agents." Although the salient effects were generally pleasant visions and a loss of the sense of time, they also reported a case of paranoid ideation, an out-of-body experience and, surprisingly, at least temporary relief from the symptoms of "neurasthenia", "nervous prostration", and "softening of the brain". Similar trials were carried out personally by medical practitioners, not with pure mescaline but with peyote tincture instead of the buttons. Detailed accounts are those of Mitchell and Eshner, who "sought so to limit the influence of mescal as to remain in full possession of (their) faculties", realizing that "the larger doses secure...more remarkable results". Nevertheless, the experiences were such that Mitchell predicted "a perilous reign of the mescal habit when this agent becomes attainable".[56]

The pioneering sexologist Havelock Ellis consumed the aqueous infusion of three mescal buttons and wrote a particularly beautiful account of his experience as a "saturnalia of the specific senses, and chiefly an orgy of vision". Having given the drug to a couple of acquaintances, he considered it "of no little interest to the physiologist and psychologist", and claimed that "for a healthy person to be once or twice admitted to the rites of mescal is not only an unforgettable delight but an educational influence of no mean value".[57] Some experiments carried out by medical personnel indicated increased tactile sensitivity after subcutaneous injection of 0.15−0.2 g of mescaline sulfate.[58] Assuming that the earlier experiments had been performed with insufficient doses to produce anything more, the psychologist Samuel Fernberger chewed and swallowed six mescal buttons. He recorded a number of effects that have since been recognized as hallmarks of psychedelic experience, reporting increased and distorted visual, tactile, and auditory sensations and his sense of time which, nevertheless, he was still able to judge in their real dimension.[59]

The response to mescaline in different species originally included both central and peripheral effects that were considered similar to those elicited by other cactus alkaloids. These effects comprise partial or total cardiac arrest and respiratory failure, combined in humans with psychotropic effects, including diffuse anxiety, (mainly visual) hallucinations with closed eyes, motor dysfunction, intensification of color patterns, and spatial distortion.[60] Mescaline can also induce hyperexcitability and complex alterations in motor behavior in small vertebrates, including frogs, rabbits, cats, and dogs,[13,61] effects that may be experienced to some extent by humans after ingesting mescal buttons, but the psychotropic experience remains the most relevant according to Buchanan's 1929 review.[62] A detailed history of the "mescaline intoxication", with references to Sahagún's 16th century chronicles and the vicissitudes of peyote use under the Spanish inquisition up to the rise of the peyote religion in the United States, was published by Beringer in 1927.[48] Noteworthy observations dating from this period were that administration of mescaline (or peyote) to individual subjects on different occasions could elicit very different effects and that during these they were generally aware that what they were experiencing was drug-induced and transient.

After the first synthesis of mescaline,[31] experimentation with mescal buttons or their extracts effectively ended, and the pure drug became available in any desired amount, opening a path for practically unlimited pharmacological and psychological experimentation.[48] Thus, clinical studies with mescaline attempting to better understand the "hallucinating state" and/or the basis of psychosis in normal subjects and psychiatric patients were subsequently carried out with valuable results,[63,64] prompting the controversial idea of using this drug as a tool to study the molecular and clinical nature of psychosis. This received moderate attention during the ensuing decades and has been reviewed recently, now as an alternative for the development of more effective strategies to treat schizophrenia.[65,66] Indeed, some evidence is consistent with the notion that an acute psychedelic experience with mescaline may be

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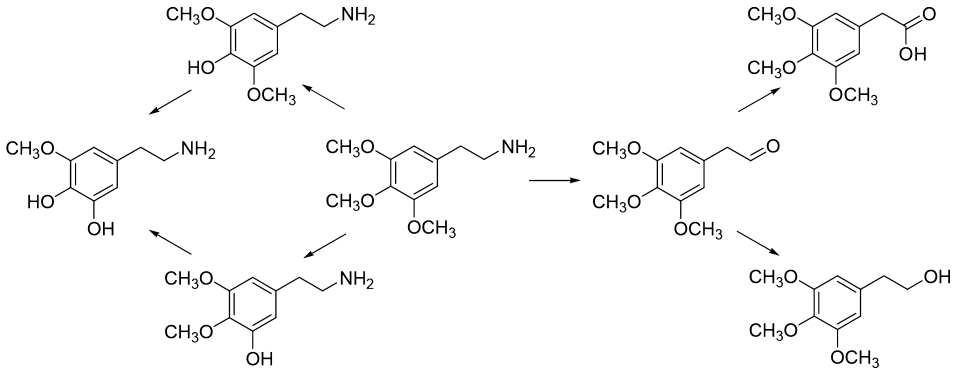
Scheme 4. Major Metabolic Modifications of Mescaline (According to Ref 104)



similar to acute schizophrenia, involving striato-limbic hyperactivity in the right brain hemisphere.[67−69] Involvement of the right hemisphere plus frontal lobe hyperactivity was later confirmed in normal volunteers after mescaline ingestion.[70] Early experimental evidence obtained in rodents demonstrated that mescaline possesses a mixed serotonergic and dopaminergic mechanism of action, as standard psychomotor responses in rodents could be blocked administering either methysergide or haloperidol, and actions on serotonergic and dopaminergic receptors were implicated.[71,72] Nevertheless, work performed in rodents further demonstrated the involvement of 5-HT_2 receptors in eliciting the psychotropic effects of mescaline, as shown by drug discrimination studies.[73] Early evidence indicating a mescaline-mediated blockade of the action of α-adrenergic receptor agonists suggested a supplemental catecholaminergic mechanism of action,[74] and much later evidence supported this notion, as similar to LSD, significant binding to α_{2A} and 5-HT_{1A} receptors was reported, although without the D_2 dopaminergic component. In this regard, one may assume that mescaline binds mainly to 5-HT_{1A}, 5-HT_{2A}, and α_{2A} receptors with little to no other receptor/transporter interactions.[75]

Despite its relevance as a naturally occurring psychotropic alkaloid serving as a structural template and a pharmacological benchmark for the in vivo characterization of an impressive number of synthetic psychedelics and the corresponding structure−activity relationship studies,[76−79] pharmacological research on mescaline remained limited to fragmentary, nonsystematic work. In contrast to modern scientific enquiry into the mechanism of action of other serotonergic psychedelics in humans,[51,80−83] there is no recent research on mescaline. This may be because slight structural modifications provided much more potent and therefore more attractive 4-substituted 2,5-dimethoxyphenylisopropylamines. In this regard, it has generally been assumed that mescaline and its phenethylamine and phenylisopropylamine congeners should have the same mechanism of action in the central nervous system, although users of different psychedelics report drug-related differences in their subjective experiences.

Early evidence supported the idea that hallucinations induced by mescaline (but possibly not by its more potent derivatives) resemble the hallucinating states achieved in patients by hypnosis.[84] These complex effects were consistent with experimental in vitro evidence indicating that mescaline may either activate or depress cortical serotonergic and noradrenergic neurons in a different "mode" compared to typical excitatory effects elicited by glutamate or acetylcholine and inhibitory effects induced by glycine or GABA. These data were the first to suggest that mescaline and LSD do not necessarily share the same mechanism of action.[85] Later evidence showed that administration of mescaline enhanced the firing of noradrenergic neurons in the locus coeruleus in response to sensory stimuli and that this activity continued without further stimulation.[86] Electrophysiological and behavioral evidence seem to agree with the notion that the disruption of (mainly) pyramidal cortical neurons located in layer V is responsible for both alterations in sensory processing and disruption of cognitive processes, as a result of the modulation of signal transduction at serotonergic 5-HT_{2A} receptors.[87]

Psychedelic effects might also involve functional selectivity in 5-$HT_{2A/2C}$ receptors that could generate differential activation of signal transduction pathways to achieve their characteristic central effects. Mescaline appears to be nonselective toward inositol triphosphate (IP_3) and arachidonic acid release.[88] Studies involving other signal transduction pathways such as β-arrestin recruitment are still lacking. The mode of activation by classic hallucinogens should differ from others elicited by nonpsychedelic substances that are also 5-$HT_{2A/2C}$ agonists associated with concomitant cluster-like activation of metabotropic glutamate receptors.[89]

The in vivo behavioral effects of mescaline in animal models were documented more than 40 years ago and described as "less consistent" compared to those of other structurally related psychedelics. The effects reported in rodents included hypolocomotion, increases of acoustic and tactile startle reactions,[90,91] and disruption of the temporal distribution of investigatory responses.[92,93] Mescaline was described to increase the head-shake (or head-twitch) response in rodents,[94] a distinctive behavioral hallmark of serotonergic psychedelics that may be elicited by activation of central serotonergic 5-HT_{2A} receptors,[95] validated several decades ago using drug discrimination.[96] This response has remained as one of the most relevant behavioral effects elicited by psychedelics in rodents, including mescaline.[97] In contrast, no effects on rearing or grooming behavior were reported.[98] Psychomotor effects elicited by mescaline may be blocked by pretreatment with 5-HT_2 antagonists, as is the case for behavioral effects elicited by other phenylalkylamine psychedelics.[99] Prepulse inhibition experiments in rats showed that mescaline may decrease this response, indicating a disruption in sensorimotor gating. Moreover, it was postulated that the former behavioral characterization should consider its pharmacokinetics and exhibited a dose-dependent biphasic effect on locomotion (at doses higher than 100 mg/kg in rats) and a delayed onset of behavior for mescaline compared to other hallucinogens.[100] Low doses of mescaline (as well as other phenylalkylamines)

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elicited hyperlocomotion in mice, attributed to the activation of 5-HT_{2A} receptors, while high doses decreased locomotion, presumably by activating 5-HT_{2C} receptors, resulting in a bell-shaped dose−response function.[101,102]

Mescaline is eliminated almost completely from the human body within 48 h, mostly unchanged, with a half-life of about 6 h. The urinary excretion, following the oral administration of [^{14}C]mescaline, peaked at the second hour.[103] The major aspects of the metabolism of mescaline were summarized in Castagnoli's 1978 review.[104] Oxidative modifications predominate, as shown in the chart (Scheme 4), which summarizes the results in several mammalian species, including humans.

Of these, oxidative deamination to 3,4,5-trimethoxyphenylacetaldehyde seems to be the most important process, leading subsequently to the acid and the alcohol. *N*-Acetylmescaline and the corresponding *N*-acetyl-*O*-demethylated derivatives have been found in different species, but this metabolic route seems to be minor in most cases. Nevertheless, in the experiments in humans with labeled mescaline, the radioactivity of cerebrospinal fluid increased for up to 5 h, and although unchanged mescaline still made up about half of the counts, *N*-acetylmescaline and *N*-acetyl-3,4-dimethoxy-5-hydroxyphenethylamine were the most abundant metabolites.[103] Phase II metabolism leading to conjugation of the ring-hydroxylated metabolites seems to be present but is also relatively unimportant.[103,105]

Mescaline is oxidized little if at all by the amine oxidase of rat brain, liver, or kidney.[106] A rabbit liver preparation was used to study the properties of the "mescaline oxidase", which was shown to produce ammonia and hydrogen peroxide aside from the phenylacetic acid,[107] but it does not seem to be an FAD^+-containing monoamine oxidase (MAO). Oxidative demethylation also occurs in rabbit liver,[108] and in rabbit lung homogenate, this activity is enhanced in the presence of semicarbazide, a monoamine oxidase inhibitor.[109] The minor metabolite 3,4-dihydroxy-5-methoxyphenethylamine is methylated to 3,5-dimethoxy-4-hydroxyphenethylamine by catecholamine *O*-methyl transferase (COMT),[110] and a very small amount of 3,4,5-trimethoxybenzoic acid was later identified as an additional urinary metabolite.[111]

Investigation into the human pharmacokinetics and metabolism of mescaline seems to have come to a standstill after 1978. A question that was occasionally raised up to that time was if the pharmacology of mescaline might be due to one or more of its metabolites.[104] Several of these failed to mimic the alkaloid in an operant discrimination test.[112] This study did not address the possibility that peripherally administered mescaline metabolites might not reach the brain in sufficient concentrations, while their formation in this organ, suggested by the abundance of *N*-acetyl-3,4-dimethoxy-5-hydroxyphenethylamine in human cerebrospinal fluid,[103] might have some effect. Another line of research that is still untouched and which may be relevant to the effects of peyote and wachuma should determine if and how the sometimes abundant companion alkaloids of mescaline may affect its distribution and metabolism.

The mescaline structure served as a template for the design of a very large number of analogues tested in humans,[78] to which conformationally restricted molecules and the "superpotent" NBOMe compounds were added in the past decade.[75,113−117] Although in 1950 it was thought that "the slightest structural changes destroy the typical effects of mescaline",[118] it was not long before racemic α-methylmescaline (TMA, 3,4,5-trimethoxyamphetamine) was tested in humans and found to be somewhat more potent in a visual test.[119,120] More extensive testing of this derivative showed that it resembled mescaline in some aspects, but its emotional responses were quite different and devoid of mescaline's "enhanced capacity for empathy" and were very variable.[121] Also, while 3,4-methylenedioxyphenethylamine is not known to be orally active, its racemic α-methyl derivative (MDA, methylenedioxyamphetamine) was initially considered to produce a mescaline-like syndrome.[119] Later, however, "doses of 150 mg of MDA produced none of the perceptual alterations or the depersonalization which had been anticipated, but it did cause heightened affect, emotional empathy and access to feelings...".[122] This description, and the subsequent use of MDA in therapy, suggest the term "entactogenic" coined to describe the activity of the MDA homologues *N*-methyl-1-[3,4-(methylenedioxy)phenyl]-2-aminopropane (MDMA, ecstasy), 1-[3,4-(methylenedioxy)phenyl]-2-aminobutane, and its *N*-methyl derivative.[123] In this regard, it is noteworthy that 2C-B (4-bromo-2,5-dimethoxyphenethylamine), which elicits mescaline-like visual experiences at doses above 15 mg, has been described as an "entactogen with psychedelic properties".[124,125]

These examples illustrate the difficulties that defining psychotomimetic or hallucinogenic entails and support the preference of the term psychedelic.[126,127] All these words imply human subjective experiences, hard to reconcile with a "rage reaction" or spontaneous brain electrical activity in cats, disruption of rope climbing by rats, or other animal models. In later years, stimulus generalization by rats trained to respond to known drugs, head shakes or twitches in rats or mice, or a panel of several different behavioral responses have been used to identify psychedelic compounds, but none of these approaches is entirely satisfactory. Therefore, what we know about the structure−activity relationships of these compounds in such models may not faithfully reflect human drug experiences.

An early generalization was that "an isopropyl side chain and triple methoxy substitution provide optimum activity", and that an *ortho* methoxy group usually enhances the compounds' potency.[128] That study included the most potent analogue identified until then, the recently discovered 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM, STP), considered to be 80−100 times more potent than mescaline.[78] The 2,5-dimethoxy substitution pattern with a small hydrophobic substituent at C-4 of the benzene ring of the amphetamine-like analogues has since been acknowledged as near-optimal to elicit the sought-for psychedelic effects.

An important development regarding the conformation in which mescaline and related substances bind to the 5-HT_{2A} receptor resulted from cyclization of the side chain, giving a derivative whose *R* enantiomer was 3−5 times as potent as mescaline, equally efficacious as a 5-HT_{2A} ligand in vitro, and also more potent in a rat drug discrimination paradigm.[129] Subsequent work on analogues of 1-(4-bromo-2,5-dimethoxyphenyl)-2-aminoethane showed that, although the (racemic) aminomethylindan derivative exhibited only modest potency, the *R*-benzocyclobutene derivative was extraordinarily potent, similar to LSD in rat discrimination experiments (Figure 2).[130]

The result of tethering the C-3 methoxyl group or both the C-3 and C-5 groups of the isopropylamine analogue of mescaline (TMA) forming dihydrofuran rings was somewhat disappointing.[131] In the 2,5-dimethoxy-4-X series, this mod-

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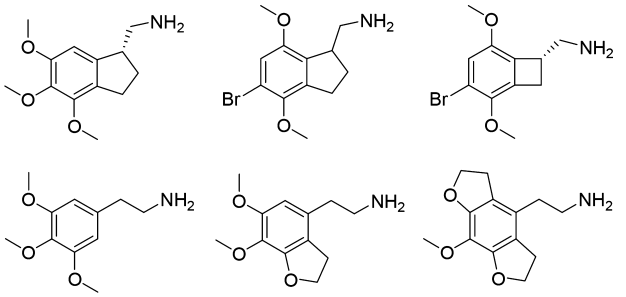

Figure 2. Mescaline and conformationally restricted analogues.

ification had led to more potent derivatives, which was explained by the favorable orientation of the oxygen lone pairs for hydrogen bonding with serine residues in the 5-HT_{2A} receptor's active site.[132,133] In the case of the 3,4,5-trioxygenated compounds, binding studies at 5-HT_{2A} and 5-HT_{2C} receptors revealed somewhat higher affinities than mescaline but, in phosphoinositide hydrolysis assays (only for 5-HT_{2A}), lower efficacies relative to serotonin and the full agonist mescaline (60 and 45%, respectively). More striking, however, was the observation that the new compounds did not fully substitute for LSD in LSD-trained rats, and at doses well above the mescaline EC_{50}, only 50 and 29% appropriate responding was recorded. In view of this unexpected result, 3,5-dimethoxy-4-ethoxyphenethylamine (escaline), which is considerably more potent than mescaline in humans,[128] was also tested. It was found to have about twice the affinity of mescaline for 5-HT_{2A} receptors and was a complete agonist with very similar functional potency, but again it failed to substitute completely for LSD in the drug discrimination experiments.

Taken together, some features of mescaline's pharmacology stand out from the currently available data. First, despite its lower in vivo potency, mescaline elicits an altered state of consciousness in nonschizophrenic subjects that may be comparable to schizophrenic psychosis. Second, its potentially different receptor interaction profile and its distinctive behavioral profile in rodents suggest a more complex mechanism of action that is still not fully understood. Third, similar to other serotonergic psychedelics such as LSD and psilocybin,[49,51,134−136] mescaline may also have therapeutically useful properties that should be explored, as ancient tradition seems to suggest. More research is required to understand the links between these relevant aspects of the pharmacology of mescaline, and the time has finally come for renewed clinical work on this alkaloid and on its still superficially studied analogues.

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