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Mescaline: The forgotten psychedelic☆

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ABSTRACT

Introduction: Mescaline (3,4,5-trimethoxyphenethylamine) is one of the oldest hallucinogens, with evidence of use dating back 5700 years. Mescaline is a naturally occurring alkaloid found in cacti, mainly in the peyote cactus (Lophophora williamsii) and in the cacti of the Echinopsis genus. Since the prohibition of psychoactive substances in the early 70s, research on mescaline and other classical psychedelics has been limited.
Objectives: This article aims to review the pharmacology and behavioural effects of mescaline, focusing on preclinical and clinical research.
Findings: Mescaline is a serotonin 5HT2A/2C receptor agonist, with its main hallucinogenic effects being mediated via its 5HT2A receptor agonist action. It also exerts effects via agonist binding at α1A/2A noradrenaline and D1/2/3 dopamine receptors. Overall, mescaline has anxiolytic-like effects in animals and increases prosocial behaviour, locomotion, and response reactivity. In humans, mescaline can induce euphoria, hallucinations, improvements in well-being and mental health conditions, and psychotomimetic effects in a naturalistic or religious setting.
Conclusion: The pharmacological mechanisms of mescaline are similar to those of other classical psychedelics, like psilocybin and lysergic acid diethylamide (LSD). Mescaline appears to be safe to consume, with most intoxications being mild and easily treatable. Improvement in mental well-being and its ability to overcome alcoholism render mescaline potentially beneficial in clinical settings.
This article is part of the Special Issue on ‘Psilocybin Research’.

1. Introduction

Psychedelics have been used for centuries in rituals or for therapeutic purposes, dating back to 8500 BC, with their use being widespread in current days (Dinis-Oliveira et al., 2019; El-Seedi et al., 2005). The use of classic psychedelics induces changes in perception and emotions that can be presented in the form of illusions (sensory distortions) or hallucinations (e.g., visual, auditory, olfactory) without the risk of addiction (Dinis-Oliveira et al., 2019; Cumming et al., 2021), although there is less evidence of this for mescaline (3,4,5-trimethoxyphenethylamine). Despite their popular use during the 60s and 70s, the prohibition of psychedelics in the early 70s restrained future research on their effects and their use as potential medical therapies (Bogenschutz and Johnson, 2016). For the purposes of this review, we use the term “psychedelics” to refer to substances that act predominantly on the 5HT2A receptor. These are often termed “classical psychedelics” and include psilocybin, lysergic acid diethylamide (LSD), dimethyltryptamine (DMT; ayahuasca), and mescaline.

Recently, the use of classical psychedelics has been proposed to be effective in a variety of psychiatric disorders such as alcoholism, depression, post-traumatic stress disorder, and obsessive-compulsive disorder (Albaugh and Anderson, 1974; Carhart-Harris et al., 2018, 2021; Krebs and Johansen, 2012; Mitchell et al., 2021; Moreno et al., 2006; Sessa et al., 2021). However, although a plethora of clinical research has been conducted on classical psychedelics, clinical studies involving mescaline have been somewhat limited. Though a significant

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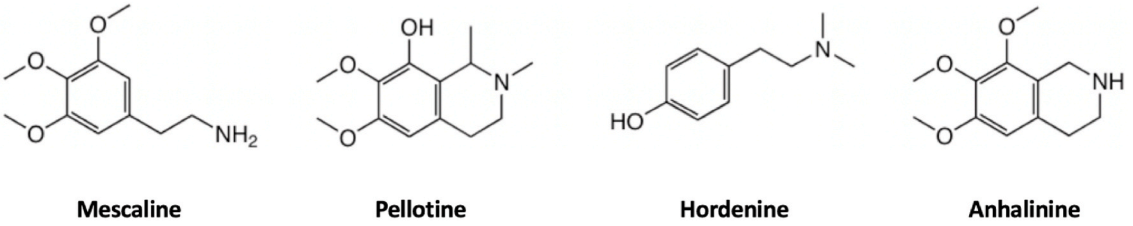

Fig. 1. Chemical structure of mescaline and other alkaloids found in the Peyote cactus (*Lophophora williamsii*).

Table 1
Receptor and monoamine transporter binding affinity of mescaline.

Receptors	Binding Affinity (Ki; μM)
5HT1A	4.1
5HT2A	6.3
[c] **5HT2B**	0.8
5HT2C	17
α1A	>15
[a]**α2A**	1.4 (antagonist)
D1	>14
D2	>10
D3	>17
[b] **mouse TAAR1**	>4.2
[b] **rat TAAR1**	>3
DAT	>30
NET	>30
SERT	>30

*Table adapted from Rickli et al. (2016)..
[a] Clemente and de Paul Lynch, 1968.
[b] Kolaczynska et al., 2022.
[c] Ray (2010)..

amount of work was conducted to investigate the effects of mescaline in the early 20th century, prohibition has limited clinical research in the past fifty years. Notwithstanding the sparse clinical data involving mescaline, Indigenous Peoples/American Indians have been using mescaline for many centuries in religious ceremonies and to treat physical illnesses like snakebites, burns, wounds, rheumatism, toothache, and fever (Carstairs and Cantrell, 2010; McCleary et al., 1960), thus providing insights into the potential health benefits of this compound.

Mescaline is a naturally occurring alkaloid that belongs to the phenylalkylamine class of compounds (Halberstadt et al., 2013). Radiocarbon dating places the use of mescaline approximately 5700 years ago for religious rituals due to its psychotropic effects or for medical purposes (Bruhn et al., 2002; El-Seedi et al., 2005; Halpern et al., 2005). Despite the illegal status of mescaline, mescaline use has been legal for religious ceremonies in the Native American Church (NAC) since 1920 and has spread ever since as far as Saskatchewan, Canada (Halpern et al., 2005; Carstairs and Cantrell, 2010; Cassels and Sáez-Briones, 2018). In 1896, the German chemist and pharmacologist Arthur Heffter was the first to isolate mescaline (Heffter, 1896). Several years later, in 1919, Ernst Späth, an Austrian chemist, synthesised mescaline by converting 3, 4,5-trimethoxybenzoic acid into its aldehyde and then into mescaline (Späth, 1919).

Naturally occurring mescaline is mainly found in cacti and, more specifically, the North American peyote cactus (Lophophora williamsii), South American San Pedro cactus (based on St. Peter's role as the gatekeeper to heaven) (Echinopsis pachanoi), the Peruvian torch (Echinopsis peruviana), Bolivian torch (Echinopsis lageniformis), and Pereskia aculeata (Ogunbodede et al., 2010; Cassels and Sáez-Briones, 2018). Mescaline is also found in some members of the Fabaceae family, like Acacia berlandieri (Clement et al., 1997).

Mescaline is not the only alkaloid found in the peyote cactus (Fig. 1). Several additional alkaloids are also found in the cactus, which are thought to enhance the effects of mescaline, although some when taken on their own, do not present with any pharmacological activity (Dinis-Oliveira et al., 2019). Aside from mescaline, common alkaloids found in the cacti identified above include pellotine, the second most abundant alkaloid in the peyote cactus and known for its sedative/hypnotic properties (Heffter, 1898). Hordenine, another alkaloid found in peyote, has antibiotic properties, but it is also used as a forensic qualitative and quantitative marker for beer (Kapadia and Fayez, 1970). As hordenine is also found in barley (Hordeum vulgare), especially during the malting of its grains, it can also be found in beer and be detected in human blood and urine following beer consumption (Steiner et al., 2016). Thus, hordenine can be used to prove beer consumption in forensic toxicology (Steiner et al., 2016) Anhalinine is a stimulant alkaloid also found in peyote (Ghansah et al., 1993).

2. Preclinical research

2.1. Receptors

Unfortunately, mescaline has not been very well studied compared to other psychedelics or novel therapies. It does not appear to have been put through standard receptor screens, so the data we have is largely derived from small single laboratory studies that have not generally used other psychedelics as comparators. The limited data we have is shown in Table 1, from which it appears that mescaline is a serotonin 2A/C (5HT2A/C) receptor agonist, with a higher affinity for the 5HT2A receptor (5HT2A EC50 = 10μM), but also exerts action at the adrenergic α2A receptor (Halberstadt et al., 2013; Rickli et al., 2016; Agin-Liebes et al., 2021). Mescaline binds with a low μmolar affinity to the serotonin 5HT1A/2B, adrenergic α1A, dopamine D1/2/3 and TAAR1 (trace amine-associated receptor 1 that regulates dopamine, noradrenaline, and serotonin neurotransmission) receptors. Mescaline also binds to the dopamine (DAT), norepinephrine (NET), and serotonin (SERT) transporters but with lower affinity (Table 1) (Páleníček et al., 2008; Kyzar et al., 2012; Rickli et al., 2016; Cassels and Sáez-Briones, 2018). Limited data is available for mescaline's activation potency. Mescaline exhibits an EC50 of 10μM for the 5HT2A receptor and >20 μM for the 5HT2B receptor (Rickli et al., 2016). The main hallucinogenic effects of mescaline are exerted via the 5HT2A receptor agonism (Halberstadt et al., 2013).

In anaesthetised rats, systemic administration of mescaline dose-dependently decreased the spontaneous firing of noradrenergic locus coeruleus (LC) neurons. To reach 50% suppression (ED50), 0.85 mg/kg of mescaline were required (Aghajanian, 1980; Rasmussen and Aghajanian, 1986). Simultaneously and unexpectedly, mescaline enhanced the reactivity of LC neurons following peripheral stimuli (sciatic nerve stimulation), which is thought to be mediated by the 5HT2A receptor (Aghajanian, 1980; Gorea and Adrien, 1988; Rasmussen and Aghajanian, 1986).

A study conducted by Trulson et al. (1983) using cats showed that the characteristic effects of mescaline are not only mediated via serotonergic and noradrenergic receptors but also via dopamine receptor signalling, as pre-treatment with low doses of either serotonin (methysergide) or dopamine (haloperidol) antagonists almost completely blocked the effects of mescaline (Trulson et al., 1983). Following mescaline administration in cats, a significant increase in limb flicking,

Table 2
Summary of preclinical studies, sorted by year of publication. BPM = Behavioural pattern monitor. HTR = head twitch response. LC = locus coeruleus. PPI = Prepulse inhibition. TMPA = 3,4,5-trimethoxypheny-lacetic acid. TMPA1d = 3,4,5-trimethoxyphenylacetaldehyde. 5-HIAA = 5-hydroxyindoleacetic acid.

Author(s)	Year	Study characteristics	Dosing	Core features/Main findings
Cochin, Woods, and Seevers	1951	- Female mongrel dogs (n = 4)	- Mescaline sulphate: 20 mg/kg via IV, and intramuscular injections and oral administration	- 28–46% of mescaline is excreted unchanged in the urine - The majority of mescaline is eliminated within 4.5h, with the remaining being excreted within 24h - Approximate 38% of mescaline is found in urine as TMPA - Mescaline detected in the kidneys, liver, and spleen
Freedman et al.	1970	- Male Sprague-Dawley rats (max n = 16)	- Mescaline: 5–15 mg/kg	- At low mescaline doses, the serotonin metabolite 5-HIAA decreases in the brain -At high mescaline doses, showed that at small doses, 5-HIAA increases, indicating an increase in release and/or reuptake of serotonin
Silva and Calil	1975	- Male albino mice (n = 682) - Behavioural tests: 1. HTR 2. Open-field test	- Mescaline hydrochloride: 5, 10, and 20 mg/kg	- Dose-related increase in HTR - At higher doses, HTR decreases - Reduction in defecation (open-field test) - At higher doses of mescaline locomotor activity scores decreased (open-field test)
Yamamoto and Ueki	1975	- Male and female Wistar King A strain rats	- Mescaline sulphate: 10, 50, 100 mg/kg	- Dose-dependent increased locomotor activity, with a peak at 60min and a total duration of 2h - Trend of increased rearing behaviour - Decreased preening and grooming - Dose-dependent increase of HTR, researching a peak effect at 60min
Korr	1976	- Adult male marmoset monkeys (Callithrex jacchus) (n = 6)	- 2,6-^{3}H-mescaline hydrochloride: 8 mg via i.p. injection	- Strong radiolabelling signal in the amygdala, hippocampus, cerebral cortex, and lateral geniculate body
Geyer et al.	1978	- Male Sprague-Dawley rats (n = 40–50)	- Mescaline sulphate: 5, 10, and 20 mg via i.p. injection	- Increase in tactile response magnitude indicating increased reactivity
Aghajanian	1980	-Male albino rats (n = 74)	- Mescaline hydrochloride: 0.25, 0.5, 1.0, and 2.0 mg/kg IV via the tail vein	- Dose-dependent suppression of LC spontaneous firing - ED50 = 0.85 mg/kg - Enhanced LC neuronal reactivity to sciatic nerve stimulation
Rasmussen and Aghajanian	1986	- Male Sprague-Dawley rats	- Mescaline hydrochloride: 2 mg/kg IV via the lateral tail vein	- Decreased spontaneous LC activity - Enhanced LC neuronal activation following sciatic nerve stimulation - Effects of mescaline on LC firing were reversed following the administration of selective 5HT2 receptor antagonist, ritanserin
Davis	1987	- Male albino Sprague-Dawley rats	- Mescaline: 20 mg/kg	- Increased startle response - Startle response was blocked when pre-treating with 5HT2 receptor antagonists ritanserin, ketanserin, LY 53857, and cinanserin
Watanabe et al.	1995	- Male ddN mice - Use of hepatic microsomes	- Mescaline hydrochloride:	- TMPA1d is oxidized to TMPA, mescaline's major metabolite, by hepatic microsomes - Oxidation is catalysed by cytochrome P450 2C29
Páleníček et al.	2007	-Male Wistar rats (n = 10–14) - Behavioural test: 1. PPI (startle chamber) 2. Open-field test	- Mescaline hydrochloride: 10, 20, and 100 mg/kg	- Rats: Half-life approx. 1h - Decrease in startle magnitude (100 mg/kg) at 60min - Decreased PPI at 60min - Hypolocomotion at 10 and 20 mg/kg - Hyperlocomotion at 100 mg/kg
Kyzar et al.	2012	- Adult wild-type zebrafish (*Danio rerio*) (n = 267) - Behavioural test: 1. Novel tank (anxiety, locomotion) 2. Open field (circling behaviour) 3. Shoaling test (social/group behaviour)	Mescaline: 5, 10, and 20 mg/l	- Dose-dependent anxiolytic-like and hyperactivating effect in the novel tank test - Increased shoaling behaviour in the open field test
Halberstadt and Geyer (Review)	2013			- Mescaline in rats: - Disruption of prepulse inhibition - Augmentation of the acoustic startle response - Attenuation of acoustic startle response habituation, which is blocked by 5HT2A/2C antagonists ritanserin, ketanserin, LY 53857and cinanserin - Mescaline in humans: - Speed up or slow down time or induce the feeling of timelessness
Halberstadt et al.	2013	-C57BL/6J mice (n = 9–10) - BPM paradigm	- Mescaline hydrochloride: 6.25, 12.5, 25,50, 100 mg/kg	- Mescaline exhibits an inverted U-shaped dose-response function - Low doses (25 and 50 mg/kg): delayed increase in locomotion - High doses (100 mg/kg): reduced locomotion - Locomotor activity induced by the 5HT2A receptor - Trend of dose-dependent reduction in holepoking and rearings
Rickli et al.	2016	- HEK293 cells for potency and cytotoxicity testing		- Mescaline has the lowest affinity for 5HT2A receptor relative to serotonergic tryptamines (psilocybin, DMT) and ergolines (LSD) - Binding to the 5HT2A receptor (K_i) was not associated with its activation (EC_{50}) - Low potency for mescaline, relative to its binding affinity

(*continued on next page*)

Table 2 (*continued*)

Author(s)	Year	Study characteristics	Dosing	Core features/Main findings
				- More potent binding for the 5HT2A than 5HT2C receptors - Mescaline did not interact with monoamine transporters, nor did it inhibit monoamine uptake - No cell death (cytotoxicity) was observed
Halberstadt and Geyer (Review)	2018			- Mescaline in rats: - Locomotion reduction - Reduction in investigatory behaviour (holepokes, rearings) using the behavioural pattern monitor paradigm - Mescaline in mice: - Inverted U-shaped dose-dependent reduction in investigatory and locomotor behaviour (increased locomotion at low doses and decreased in high dosed - Induction of head twitch response (HTR) in rats and mice, which is highly correlated with 5HT2A binding affinity
Halberstadt et al.	2019	- Male C57BL/6J mice - Assessing head twitch response (HTR)	Mescaline hydrochloride	- HTR induced at an ED50 of 6.51 mg/kg with an inverted U-shaped dose-response - Mescaline's potency is enhanced in its analogues with the addition of a 4-methoxy group by one or two methylene units or an α-methyl group

abortive grooming, grooming, head shakes, stares, and hallucinatory-like responses ("looking around at the floor, ceiling or walls of the cage and appearing the track objects visually, or hissing at, batting at, or pouncing at 'unseen' objects") were observed, further supporting a supplemental catecholaminergic action of mescaline (Trulson et al., 1983; Rickli et al., 2016).

2.2. Pharmacology

In cats, mescaline has an estimated half-life of 2h following the IV injection of α-[14C]-mescaline (25 mg/kg). Autoradiography with [3H]-mescaline in marmoset monkeys (Callithrex jacchus) showed that mescaline mostly accumulates in the hippocampus, amygdala, lateral geniculate and anterior cingulate cortex, persisting even for 18h post-injection (8 mg, i.p.) (Korr, 1976). LD50 for mescaline varies between species, with Rhesus macaques being the most sensitive, with a relatively low LD50 of 30 mg/kg (intravenous), followed by dogs with LD50 of 54 mg/kg (intravenous). LD50 for rats can vary from 132 mg/kg (intraperitoneal) to 534 mg/kg (subcutaneous), with death usually resulting from respiratory depression and convulsions. Mice data shows LD50 values, ranging from 157 mg/kg (intravenous) to 880 mg/kg (per os). (Freedman, 1969; Hardman et al., 1973; Kapadia and Fayez, 1970). In humans, only one death has been reported as a result of mescaline consumption, with concentrations of mescaline being 9.7, 70.8, and 1163 μg/mL in blood, liver, and urine, respectively (Reynolds and Jindrich, 1985).

Mescaline is rapidly absorbed by the gastrointestinal tract, with a large percentage of the dose being distributed to the kidneys and liver (Dasgupta, 2017; dos Santos et al., 2016; Shah et al., 1979). Combination with hepatic proteins delays mescaline's concentration in the blood and increases its half-life, resulting in a delay of its effects (dos Santos et al., 2016). Indeed, an earlier study by Cochin et al. (1951), using dogs, showed that mescaline was detected in larger amounts in the kidneys and liver relative to the blood and brain. A total of 28–46% of mescaline is excreted unmodified in the urine, with the majority of mescaline being eliminated within 4.5h and the remaining within 24h. Approximately 38% of the mescaline is found in urine metabolised to 3,4,5-trimethoxyphenylacetic acid (TMPA) (Cochin et al., 1951). The main mescaline metabolic route for many species, including humans, is via the oxidative deamination of TMPA through 3,4,5-trimethoxyphenylacetaldehyde (TMPA1d). Based on research conducted in mice, it is understood that the oxidation of TMPA1d via hepatic microsomes is required to produce TMPA, and it is catalysed by cytochrome P450 2C29 (CYP2C29) (Watanabe et al., 1995).

Recent research utilizing HEK293 cells pointed toward the importance of organic cation transporters (OCTs) and, more specifically, OCT1 in the hepatic metabolism of mescaline (Jensen et al., 2021). The presence or high activity of the highly polymorphic OCT1 could be considered advantageous as it may enhance hepatic mescaline metabolism and reduce the chances of intoxication. However, since mescaline was identified as an OCT1 substrate in vitro, we cannot be certain that such results can be translated in vivo (Jensen et al., 2021).

In a study with rats, Freedman et al. (1970) showed that at small doses, mescaline decreases the levels of the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA). At high doses, it increases 5-HIAA, which is consistent with an increase in the release and/or reuptake of serotonin (dos Santos et al., 2016; Freedman et al., 1970), although this is not proven.

Mescaline has also been shown to be safe at a cellular level. A study conducted by Rickli et al. (2016), using HEK293 cells, showed no cell damage (cytotoxicity) following the administration of phenethylamines, like mescaline, during an adenylate-kinase release assay (Rickli et al., 2016). Such evidence suggests that the risk of cellular damage associated with mescaline use in humans could be low, rendering mescaline safe for human consumption. Whilst this lack of cytotoxicity is encouraging, some drugs that act in the serotonin reuptake sites have been shown to be toxic to these neurons (Costa and Gołembiowska, 2022; Gouzoulis-Mayfrank and Daumann, 2022). This would need to be specifically evaluated for mescaline.

2.3. Animal behaviour

A number of studies have been conducted to investigate the effects of mescaline in animal models. For example, research has been conducted using zebrafish (Danio rerio), a popular model for psychoactive drug screening (Kyzar et al., 2012, 2017). Kyzar and colleagues used zebrafish to characterise the effects of mescaline (5, 10, and 20 mg/l) in the novel tank, open field (circling behaviour), and shoaling tests (social/-group behaviour). In the novel tank test, they found that mescaline exerted anxiolytic-like actions in a dose-dependent manner and induced hyperactivity (increased locomotion). In the novel tank test, mescaline also increased shoaling behaviour (swimming in a group) (Kyzar et al., 2012), suggesting a prosocial effect.

In rats, locomotion is also affected following the administration of mescaline. Overall, an increase in locomotor activity is observed following mescaline administration, with its peak effect (10 mg/kg) reached at 1h and lasting for 2h (Yamamoto and Ueki, 1975). Findings of hypolocomotion at lower doses of mescaline (e.g., 10 and 20 mg/kg) and hyperlocomotion at higher doses (e.g., 100 mg/kg) have also been made (Páleníček et al., 2008). When tested in a familiar environment, hallucinogens like mescaline increase locomotor activity and investigatory behaviour (rearing and holepoking) in rats, which indicates that in a non-threatening environment, rats feel more comfortable moving around and exploring their surroundings (Yamamoto and Ueki, 1975; Halberstadt and Geyer, 2018). Following the administration of mescaline, grooming and preening were decreased (Yamamoto and Ueki, 1975), indicating a potential anxiolytic-like action of mescaline (Kalueff et al., 2016).

Mescaline also induces a head twitch response (HTR) in rats in a dose-dependent manner, indicating its hallucinogenic effects, with a peak effect reached at 1h, following 10, 50, and 100 mg/kg of mescaline (Yamamoto and Ueki, 1975). At larger doses (e.g., 40 mg/kg), mescaline has also been shown to have depressant effects, reflected in decreased head-twitch scores (Silva and Calil, 1975). The induction of HTR is thought to be highly correlated with the 5HT2A binding affinity (Halberstadt and Geyer, 2018).

Acoustic startle and prepulse inhibition (PPI) are also classic behaviours affected in rats following mescaline administration, revealing sensorimotor gating in animals as is the case in humans (Halberstadt and Geyer, 2013). Startle response is measured using a stabilimeter to measure startle amplitude. Overall, mescaline increased acoustic startle response in rats (Davis, 1987). At high doses of mescaline (100 mg/kg), the acoustic startle response was decreased (Páleníček et al., 2008). The acoustic startle response is blocked when rats are pre-treated with 5HT2A/2C antagonists ritanserin, ketanserin, LY 53857 and cinanserin (Davis, 1987). Along with the acoustic startle response, mescaline (5, 10, and 20 mg/kg) also augments the tactile startle response evoked by air-puff stimuli, indicating an overall increase in reactivity (Geyer et al., 1978). On the other hand, PPI decreases following mescaline administration, with effects evident 1h after a single bolus of mescaline (20 mg/kg) (Páleníček et al., 2008).

In mice, the effects of mescaline can differ in some respect from the effects observed in rats. Regarding HTR, mescaline will induce head-twitch in mice with an ED50 of 6.51 mg/kg, following an inverted ‘U’ dose-response, instead of the dose-dependent response seen in rats (Silva and Calil, 1975; Halberstadt et al., 2019). This inverted ‘U’ dose-response was also seen in mice when investigating locomotor activity in a behavioural pattern monitor (BPM). Halberstadt, Powell, and Geyer (2013) showed that mescaline produced a delayed increase in locomotion at low to moderate doses (25 and 50 mg/kg), as measured by distance travelled. Locomotor activity was significantly reduced at high doses (e.g., 100 mg/kg) (Silva and Calil, 1975; Halberstadt et al., 2013). The hyperactivity induced by mescaline was completely blocked following pre-treatment with the 5HT2A receptor antagonist MDL100907. A trend of reduced investigatory behaviour (holepoking behaviour and rearings) was also observed, following a similar behavioural pattern with rats (Halberstadt et al., 2013). The same team also conducted an experiment using 5HT2A knock-out (KO) mice to determine whether locomotion increased by activating the 5HT2A receptor. Treatment with mescaline (25 mg/kg) had no effects on locomotor activity in the KO mice. However, as expected, it increased the distance travelled in the wild-type mice, supporting the importance of the 5HT2A receptor (Halberstadt et al., 2013). Summaries of all the mentioned preclinical studies have been listed in Table 2.

3. Clinical research

3.1. Kinetics

Mescaline has an average half-life of 6h in humans (Charalampous et al., 1966). According to Charalampous et al. (1966), mescaline metabolites are found in the urine, plasma, and spinal fluid. Approximately 81.4% of the mescaline oral dose in humans is secreted unchanged in the urine, and 13.2% is excreted as TMPA. Within the first 24h, approximately 87% of mescaline has been excreted, and 92% within 48h (Charalampous et al., 1966). Oral administration of mescaline may result in higher deamination via the liver relative to an IV injection with a rapid systemic distribution (Charalampous et al., 1964; Charalampous et al., 1966).

A cross-tolerance study of mescaline with other serotonergic psychedelics, like LSD and psilocybin, shows evidence of tolerance developing a few days after mescaline consumption. These effects were restored following 3–4 days of abstinence (Wolbach et al., 1962a, 1962b).

3.2. Physiological and psychological effects

Common physiological effects of synthetic mescaline include mydriasis [dilated pupils], increased body temperature, pulse rate and blood pressure, which remain high for several hours.

With over 200 mg of mescaline (synthetic or from cacti), nausea and vomiting are also observed and at times attributed to the bitter taste of the cactus when brewed or chewed (Guttmann, 1936; Denber and Merlis, 1955; Cohen, 1960; Wolbach et al., 1962a).

Following the administration of mescaline, synaesthesia [stimulation of one sense causing the production of another sense] was observed (Guttmann, 1936; Hartman and Hollister, 1963). When listening to a pure tone, under the influence of mescaline, healthy participants observed colours or other visual effects, like “brightening of the visual field or shattering patterns” (Hartman and Hollister, 1963). Others experienced colours producing certain tastes, like green producing a sweet metallic taste and blue the taste of phosphorous (Guttmann, 1936).

In general, the perception of colour was affected, with the colours being perceived as more intense. When discriminating hues, many participants made errors in hues spanning from red-yellow to green-blue (when administered 5 mg/kg synthetic mescaline) (Guttmann, 1936; Hartman and Hollister, 1963). Changes in the colours of objects would follow the altered colour perception, paving the way to true visual hallucinations, with changes in visual perception preceding the visual hallucination (Guttmann, 1936). Mescaline produces a distinct pattern of visual hallucinations, defined by a “geometrisation” or the kaleidoscopic-like nature of three-dimensional objects depicted in indigenous traditional art (Denber and Merlis, 1955; dos Santos et al., 2016). If a large dose of mescaline is given (300 mg), the hallucinations are accompanied by altered time/space/personality perception. Other sensations produced by mescaline include hypersensitivity to noise, paraesthesia in the fingertips, and loss of body orientation (Guttmann, 1936).

Time perception was highly affected by mescaline. Some perceived time as faster and others as slower, with cases also reporting the feeling of timelessness (Guttmann, 1936; Hoch et al., 1952). The feeling of euphoria (extreme bliss, ecstasy, sense of well-being) is also often present following mescaline ingestion (Guttmann, 1936; Wolbach et al., 1962a). However, mescaline can also produce feelings of anxiety, depression, panic, loss of emotions, and “splitting of personality” (ego dissolution), but these effects occur on only rare occasions (Guttmann, 1936; Cohen, 1960; Wolbach et al., 1962a; Hermle et al., 1992). In extreme cases of adverse reactions to mescaline, intravenous fluids, sodium amytal, sodium succinate, benzodiazepines, activated charcoal, and droperidol have been used to resolve the symptoms (Carstairs and Cantrell, 2010; Cohen, 1960; Denber and Merlis, 1955; Stevenson and Sanchez Jr., 1957). Psychotomimetic effects were also observed, making researchers of the 20th century believe that mescaline could be used to experimentally simulate schizophrenia (Guttmann, 1936; Denber and Merlis, 1955).

3.3. Modern neuroscience

In an early pilot study with six healthy adult males using 500 mg of mescaline sulphate and single-photon emission computed tomography (SPECT) to display regional cerebral blood flow (rCBF), Oepen et al.

(1989) found a selective increased neuronal activity, especially in the striato-limbic system of the right hemisphere, which they claimed to resemble schizophrenia neural physiology (Oepen et al., 1989). Several years later, Hermle et al. (1992) used mescaline as a model of experimental psychosis. Twelve healthy male volunteers were given orally 500 mg of mescaline sulphate. Participants completed neuropsychological and cognitive tests and a face/nonface decision task known to have a right-hemisphere location. SPECT was also utilised in this study to measure the anterior versus posterior cerebral and limbic activity. They found that mescaline produced an acute psychotic state 3.5–4h following its ingestion. Right hemisphere imbalances, with a deterioration of the left visual field as psychopathology increased, were also observed, along with improved functions in the opposite brain areas, i.e., the left hemisphere and right visual field. During the face/nonface decision task, increased rCBF in the right anterior cortical regions ("hyperfrontal" pattern) and decreased right hemisphere performance were evident (Hermle et al., 1992, 1998).

3.4. Therapeutic studies

In the mid-50s, Herman Denber and Sydney Merlis gave intravenously 500 mg of synthetic mescaline sulphate to twenty-five patients diagnosed with schizophrenia to investigate its therapeutic potential. Out of all the participants, only one patient reached complete remission (and was still well at 1 year), three patients achieved temporary remission, and the remaining twenty-one patients experienced reactivation or worsening of their psychotic symptoms (Denber and Merlis, 1955). Shortly after, Sydney Merlis followed up on this study and administered between 500 and 750 mg of mescaline sulphate to twenty-four patients with chronic schizophrenia. He found that only one patient had improved enough and was fit for discharge. Seven patients experienced temporary improvement, with the rest of the participants exhibiting no change in their symptoms though strangely non worsened (Merlis, 1957).

Although these studies showed that mescaline did not seem to have any therapeutic potential for schizophrenia, several years later, Albaugh and Anderson, in 1974, published an article supporting the potential use of mescaline in the treatment of alcoholism. The study focused on Indigenous Peoples/American Indians who suffer from alcoholism. The therapeutic approach examined in this report was a combination of group meetings, cultural therapy, and participating in NAC meetings with and without peyote/mescaline. On average, people taking part in the peyote ceremonies of the NAC will consume the equivalent of 500 mg mescaline/11 peyote buttons (~45 mg mescaline/button). Discussion about alcoholism and the cathartic expression of emotions during the ceremonies were helpful steps for the participants to overcome their alcoholism. American Indians participating in these ceremonies experienced a carry-over effect of openness and willingness to communicate. Many experienced that a single peyote meeting was the turning point for overcoming their alcoholism (Albaugh and Anderson, 1974). More recently, Halpern et al. compared three groups of Navajo: NAC members that had ingested peyote $\geq$ 100 times ($n = 61$) recovered alcoholics abstinent for at least two months ($n = 36$), and lifetime abstainers ($n = 79$), serving the purpose of the comparator group. Both the peyote users and comparator group scored significantly higher than the former alcoholics in psychological well-being, and the peyote users were more psychologically healthy relative to their comparator group, with better scores for anxiety, depression, loss of behavioural/emotional control, psychological distress, and mental health index (Halpern et al., 2005).

Further support for mescaline's potential for improving mental health has been provided by an international survey published in 2021. The study examined whether mescaline use in non-clinical settings was associated with improving symptoms of mental illnesses such as depression, anxiety, post-traumatic stress disorder (PTSD), and alcohol/drug use disorder, as seen by self-reports. A total of 452 people

Table 3
Comparing mescaline with classic psychedelics LSD and psilocybin.

	Mescaline	LSD	Psilocybin
Dose (average)	200–500 mg	0.05–0.2 mg	20–40 mg
Potency compared with mescaline	–	2000x stronger	20x stronger
[a] **$5HT_{2A}$ affinity (Ki; μM)**	6.3	0.004	0.06 (psilocin)
Onset of effects	1–3h	30–40 min	20–30 min
Duration of effects	>10–12h	8–12h	4h

*Table adapted from Dinis-Oliveira et al., 2019.
[a] Ki values taken from Rickli et al., 2016 and Passie et al., 2002.

Table 4
Summary of clinical studies, sorted by year of publication.

Author(s)	Year	Study characteristics	Dosing	Core features/Main findings
Guttmann	1936		- Synthetic mescaline	- Physiological effects: mydriasis [dilated pupils], increased body temperature and increased pulse rate and blood pressure - Synaesthesia - Change in colour perception and hue discrimination - Visual hallucinations - Altered time perception (too fast, too slow, or timeless) - Euphoria - Rare occasions: anxiety, depression, panic, loss of emotions, and ego dissolution
Denber and Merlis	1955	- Twenty-five participants: eighteen female and seven male schizophrenic patients	- Mescaline sulphate: 500 mg IV	- One patient: complete remission - Three patients: temporary remission - Twenty-one patients: reactivation or worsening of psychotic symptoms - Several minutes post-injection: "Nausea, retching, vomiting, sweating, generalized discomfort, feelings of heat, cold, and choking, a "peppermint" taste in the mouth, palpitations, chest and neck pains, and dyspnoea" - Most frequent affective symptoms: "anxiety, restlessness, uneasiness, apprehension, tension and panic"
Cohen	1960		-Mescaline: 200–1200 mg	- Adverse responses tend to appear at high doses (>400 mg) - Less frequently: nausea and vomiting - IV sodium amytal or chlorpromazine

(continued on next page)

Table 4 (*continued*)

Author(s)	Year	Study characteristics	Dosing	Core features/Main findings
Wolbach et al.	1962	- Ten former morphine addicts	-Received in randomized order: a) Mescaline hydrochloride: 2.5 mg/kg and 5.0 mg/kg b) LSD: 0.75 mcg/kg and 1.5 meg/kg	- Induced increased body temperature, systolic blood pressure, pupillary diameter and decreased the kneejerk threshold - Induction of anxiety, euphoria difficulty in thinking and concentration, alterations in sensory -visual- perception leading to both pseudo- and true hallucinations - Mescaline peak effects: 2–2.5h post-dosing
Hartman and Hollister	1963	- Eighteen volunteers -Three groups of six: a) people naïve to drug effects and psychological concepts b) graduate students in psychology c) graduate students without knowledge of the drugs and measured variables	-Mescaline: 5 mg/kg (- LSD-25: 1 μg/kg - Psilocybin: 150 μg/kg)	- Mescaline increased errors in colour (hue) discrimination in red-yellow and green-blue areas - Mescaline (and LSD-25) elicited more colours in response to the flicker
Charalampous et al.	1964	- Twelve healthy adult males	- Mescaline hydrochloride: 350 mg	- Trimethoxyphenylacetic acid (TMPA) was found in urine
Charalampous, Walker and Kinross-Wright	1966	- Twelve healthy adult males	- Mescaline hydrochloride: 500 mg	- 81.4% of the dose is eliminated unchanged in the urine within the first hour - 13.2% of the dose is excreted as 3,4,5-trimethoxyphenyl-acetic acid (TMPA) within the first hour - 87% of the dose was eliminated within the first 24h and 92% within 48h
Albaugh and Anderson	1974	- American Indians from the Cheyenne and Arapaho tribes - 30-day inpatient programme at the Clinton Indian Hospital in Oklahoma	- Peyote buttons (average: 11 buttons, 45 mg mescaline each) - Average mescaline: 500 mg	- Therapeutic approach: group meetings, cultural therapy, and taking part in meetings at the Native American Church (NAC), with and without peyote/mescaline - Discussion about alcoholism and emotions during the ceremonies was helpful in overcoming alcoholism - Carry-over effect of 7–10 days post peyote of openness and willingness to communicate
Oepen et al.	1989	- Six healthy adult men - Single photon emission computed tomography (SPECT) to measure regional cerebral blood flow (rCBF)	- Mescaline sulphate: 500 mg	- Increased rCBF in the striato-limbic regions of the right hemisphere - Decreased right hemisphere performance during face/nonface decision task
Hermle et al.	1992	- Twelve healthy males - Open study - Higher education (academics) - Single photon emission computed tomography (SPECT) to measure regional cerebral blood flow (rCBF)	- Mescaline sulphate: 500 mg	- Mescaline produced an acute psychotic state 3.5–4h post-drug intake - Increased rCBF in the right anterior cortical regions (“hyperfrontal” pattern) - Decrease in right hemisphere performance during face/nonface decision task
Hermle et al.	1998	- Twelve healthy male volunteers	- Mescaline sulphate: 500 mg	- Acute psychotomimetic state 3.5–4h post mescaline ingestion - Decrease in right hemisphere performance during face/nonface decision task
Halpern et al.	2005	- Sixty-one Native American Church (NAC) members with ≥100 times peyote use - Thirty-six recovered alcoholics (min two months abstinent) - Seventy-nine lifetime abstainers		- Peyote users were more psychologically healthy relative to the comparator group - Better scores for anxiety, depression, loss of behavioural/emotional control, psychological distress, and mental health index
Carstairs and Cantrell	2010	- Thirty-one cases of peyote/mescaline use between 1997 and 2008 in California		- Mescaline effects: sympathomimetic toxidrome (tachycardia, agitation, pupillary dilation), hallucinations - Therapeutic interventions for adverse mescaline effects: benzodiazepines, intravenous fluids, activated charcoal, droperidol
*Agin-Liebes et al.	2021	- International epidemiological study - 452 participants (online survey)		- Participants with reported improved anxiety were significantly younger than those without improvements/worsening following mescaline use - Participants with previous psychiatric conditions reported improvement following their most memorable experience (Improvement in a) depression = 86% (n = 184), anxiety = 80% (n = 167), PTSD = 76% (n = 55), alcohol misuse/use disorder = 76% (n = 48), drug misuse/use disorder = 68% (n = 58)) - 2–5% of participants with psychiatric conditions reported intentions to address/resolve their condition with mescaline
*Uthaug et al. *Agin-Liebes et al. and Uthaug et al. are utilizing the same dataset	2021	- International epidemiological study - 452 participants (online survey)		- Oral self-administration for spiritual and nature connection - 48% reported having the most memorable experience with San Pedro with a moderate to high dose (8–13h) - Participants with previous psychiatric conditions reported improvement following their most memorable experience (Improvement in a) depression = 86%, anxiety = 80%, PTSD = 76%, alcohol misuse/use disorder = 67%, drug misuse/use disorder = 68%)

completed the survey, gathering information regarding their mescaline use and experience and previous mental illness diagnosis. Improvement was observed in 86% of people with depression (n = 184), 80% in those with anxiety (n = 167), 76% in PTSD (n = 55), 76% in alcohol misuse/use disorder (n = 48), and 68% in drug misuse/use disorder (n = 58). Improvement in mental health conditions was accompanied by higher scores in mystical experiences (MEQ-30), psychological insight questionnaire (PIQ), and the ego dissolution inventory (EDI). Such evidence indicates that using mescaline in a naturalistic setting could improve several psychiatric disorders (Agin-Liebes et al., 2021; Uthaug et al., 2021). Summaries of all the mentioned clinical studies can be found in Table 4.

However, all these data are of limited value as they are not conducted using randomised double-blind controlled methodologies. Modern studies are clearly needed before we come to any conclusions about mescaline's clinical utility.

4. Conclusion

Mescaline acts similarly to other classical psychedelics: despite its lower potency, mescaline is a 5HT2A receptor agonist, which is thought to be how it exerts its hallucinogenic effects, as do other serotonergic psychedelic substances (Table 3). Aside from binding to the 5HT2A receptor, mescaline also has activity on other receptors, including the adrenergic α1A/2A and dopaminergic D1/2/3 receptors, which likely explains its distinctive behavioural profile. In addition, mescaline can induce an altered state of consciousness, which can sometimes contain symptoms also observed in schizophrenia. Mescaline also has a longer half-life than many other serotonin psychedelics.

Self-reported improvements in mental well-being and the ability to overcome alcoholism following mescaline use in naturalistic or religious settings suggest therapeutic potential. However, more research is required to define its potential clinical use.

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IAV is a paid intern for Neural Therapeutics with shares. DJN is a consultant for Neural Therapeutics paid with shares. IC is employed by Neural Therapeutics and JRBD, and KADN are on the board of "Neural Therapeutics Inc."

Data availability

No data was used for the research described in the article.

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