Psychopharmacology (2008) 196:51–62
DOI 10.1007/s00213-007-0926-5

ORIGINAL INVESTIGATION

Mescaline effects on rat behavior and its time profile in serum and brain tissue after a single subcutaneous dose

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Received: 16 April 2007 / Revised: 14 August 2007 / Accepted: 21 August 2007 / Published online: 7 October 2007

Abstract
Rationale Mescaline is a nonselective serotonin receptor agonist. It has relatively delayed onset of action and prolonged duration. Mescaline attenuates various behavioral parameters in rats; however, no information is available about its pharmacokinetics in rats and its relation to the behavioral changes produced by the drug.
Objectives The present study evaluates the spontaneous locomotor activity and sensorimotor gating in relation to mescaline concentrations in the serum and the brain of rats
Materials and methods Behavioral changes induced by mescaline [10, 20, and 100 mg/kg subcutaneously (s.c.)] were evaluated in an open-field test and testing of the prepulse inhibition of acoustic startle reaction (PPI) 15 and 60 min after drug administration. The time disposition of mescaline 20 mg/kg s.c. in rat serum and brain homogenates was analyzed by gas chromatography–mass spectrometry.
Results Mescaline produced significant inhibitory effects on locomotion in low doses and a biphasic effect with the highest dose. In the PPI test, only when tested 60 min after drug administration, all doses of mescaline disrupted PPI. Besides the experimental protocol, we have observed that approximately 50% of animals receiving 100 mg/kg died within 12 h post-injection. The serum levels of mescaline rapidly increased within 30 min and subsequently quickly decreased; however, the brain concentrations reached a maximum 1 h after administration and remained high for an additional 60 min.
Conclusions Mescaline had a delayed onset of the main behavioral changes in rats compared to other hallucinogens. Behavioral changes correlated with the pharmacokinetics of the drug.

Keywords Mescaline · Locomotion · Sensorimotor gating · Rats · Pharmacokinetics

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Introduction

Mescaline (3,4,5-trimethoxyphenethylamine) is an active compound of the hallucinogenic cacti peyote (*Lophophora williamsii*). It has a strong potency to induce altered states of consciousness in humans and produces a variety of symptoms in animals. Mescaline is a serotonin receptor agonist and shows affinities mainly to 5-HT_{1A} and 5-$HT_{2A/B/C}$ serotonin receptors (Nichols 2004; Monte et al. 1997; Harms et al. 2003). The proportion of mescaline agonism on each receptor subtype is less clear, as is the action on dopaminergic and noradrenergic systems (Monte et al. 1997; Spinella 2001; Laing and Siegel 2003; Harms et al. 2003). Due to its low lipid solubility arising from its polar molecular characteristics, mescaline does not pass through the blood–brain barrier well, and therefore, higher doses are needed relative to other hallucinogens to produce a psychotropic effect (Spinella 2001; Laing and Siegel 2003). Mescaline is reported to undergo *O*-demethylation, *N*-acetylation, and amine oxidation with different enzyme systems (Musacchio and Goldstein 1967; Scheline 1978). However, all of the metabolites are believed to be inactive (Baselt 2002). In humans, 87% of an oral dose is excreted

within 24 h and 92% within 48 h (Charalampous et al. 1966). The human plasma half-life is reported to be 6 h, and psychoactive effects may last up to 12 h (Nichols 2004; Hermle et al. 1992; Charalampous and Kinross-Wright 1963; Charalampous et al. 1966; Baselt 2002; Spinella 2001).

The behavior of rats, e.g., locomotor activity, investigatory behavior, sensorimotor gating, etc. is often attenuated by hallucinogenic drugs like DOI (2,5-dimethoxy-4-iodoamphetamine; Sipes and Geyer 1994; Sipes and Geyer 1995b), DOM (2,5-dimethoxy-4-methylamphetamine; Geyer et al. 1979; Yamamoto and Ueki 1975), LSD (*N*, *N*-diethyl-D-lysergamide; Ouagazzal et al. 2001; Palenicek et al. 2005a, b), or psilocin (Palenicek et al. 2005a, b, 2006). However, animal data from mescaline are much less consistent, and the majority of it was published more than 20 years ago. Davis (1987) has studied the effect of mescaline on acoustic startle resulting in an increase of startle reaction induced by 20 mg/kg (Davis 1987). Mescaline also increased tactile startle response magnitudes in experiments done by Geyer et al. (1978). Others described the disruption of the temporal distribution of investigatory responses by rats in a novel hole-board induced by a variety of hallucinogens including mescaline (Geyer et al. 1979) or an ataxia induced by grading doses of mescaline (Sykes 1986). Administration of hallucinogenic agents, including mescaline, also increased the frequency of head twitches of mice, decreased defecation, and did not produce any consistent changes in ambulation, rearing, or grooming in rats (Silva and Calil 1975). Several other studies mention an increase in aggressive behavior of rats after administration of mescaline (Sbordone et al. 1979; Carder and Sbordone 1975; Sbordone et al. 1978). Mescaline has also been used in drug discrimination studies. Female CFN (Carworth Farms) rats were able to discriminate mescaline from saline but not from LSD (Hirschhorn and Winter 1971). In another study, Browne et al. (1974) found that in male Sprague–Dawley rats discrimination of mescaline from saline was greatly reduced by pretreatment with nonselective serotonin 5-HT_2 receptor antagonists (Browne et al. 1974). The aforementioned studies as well as other mescaline studies used different time schedules when examining its behavioral properties. Of interest is a study published by Sethy and Winter (1973) who described that the brain concentrations of mescaline in female CFN rats peaked 30 min after intraperitoneal (i.p.) administration. In addition, another paper described that after the administration of mescaline 40 mg/kg i.p., the tissue concentrations in rat serum and liver decreased rapidly compared to in the brain where the concentrations remained high for 3.5 h (Cohen and Vogel 1970). Nonetheless, the temporal disposition of mescaline in serum and the brain in association with effects on sensorimotor gating and locomotion in animals has yet to be studied. This is a crucial point of great importance, as many previous studies, e.g., Wing et al. (1990), Geyer et al. (1978, 1979), Silva and Calil (1975) may only describe partial effects of the drug. Thus, in our study, with respect to polarity of mescaline and its delayed crossing of the blood–brain barrier, we have focused on the evaluation of kinetics as well as the latter-mentioned behavioral effects of this compound in rats.

An intact rat exhibits a number of different behavioral patterns when placed in the open field arena, such as floor- and air-sniffing, grooming, and resting, which reflect both the animal's responsiveness to the novelty of environmental stimuli and its habituation potency (Lát 1973; Eilam and Golani 1989; Golani et al. 1993). One of the most sensitive behavioral parameters to many exogenous insults is the locomotor activity of the animal (Geyer et al. 1986). This is often attenuated by many centrally active compounds and is also a sensitive marker for detecting some of the effects of hallucinogenic drugs, e.g., Geyer et al. (1979), Palenicek et al. (2005a, b), Krebs-Thomson et al. (1998, 2006), Ouagazzal et al. (2001).

Sensorimotor gating represents the ability of a weak sensory event to inhibit the motor response of an intense stimulus; it is thought to be governed by central inhibitory mechanisms (Swerdlow et al. 2001). The deficits in sensorimotor gating are frequently present in several psychiatric diseases especially in schizophrenia as well as during intoxication with hallucinogenic drugs both in man and animals (Vollenweider and Geyer 2001; Geyer et al. 2001). Sensorimotor gating can be measured by prepulse inhibition of the acoustic startle response, reflecting the ability of the brain to filter sensory information (Koch 1999). Many neurotransmitter systems as well as brain structures are involved in this reaction (Swerdlow et al. 2001; Geyer et al. 2001; Bubenikova et al. 2005), and agonists of the serotonin receptors, especially 5-HT_{2A} (Sipes and Geyer 1994, 1995b, 1997) and 5-HT_{1A} (Sipes and Geyer 1995a; Krebs-Thomson et al. 2006), reduced prepulse inhibition (PPI) in rats.

In light of the above findings and facts, we have focused our study on the behavioral effects of mescaline in a time-dependent manner in hand with its pharmacokinetic correlations. We have studied locomotor effects of graded doses of mescaline in the open filed and its effect on sensorimotor gating. To cover most of the effects of mescaline including its temporal characteristics, we have evaluated both tests in two different time schedules. Thus, two groups of animals were tested for each dose of mescaline, one 15 min and the other 60 min after the drug administration. As hallucinogens and other serotonin mimetics, e.g., mCPP (1-(m-chlorophenyl)piperazine), have inhibitory effects on locomotion (Palenicek et al. 2006;

Bankson and Cunningham 2001; Krebs-Thomson et al. 1998; Geyer et al. 1979; Krebs-Thomson and Geyer 1996), we assumed that mescaline will decrease the locomotion of rats in the open field. To evaluate the effects of mescaline on sensorimotor gating, we measured PPI of the acoustic startle reaction. As in the precedent hypothesis, we anticipated that the drug will disrupt PPI similarly to other hallucinogens. Due to its delayed onset of action, we supposed that mescaline effects will be more pronounced at 60 min than at 15 min post-administration. Congruently, to prove if we have chosen the appropriate testing periods, we have evaluated the temporal profile of mescaline disposition in rat serum and brain homogenates, and as such, we expected a delayed onset of brain tissue mescaline levels compared to serum levels.

Materials and methods

Animals

All experiments were carried out on adult male Wistar rats (SPF animals; Hannover breed Konárovice, Czech Republic) weighing 200–250 g. In behavioral experiments, 10–14 animals were used in each experimental group. For kinetic disposition study, four groups consisting of six animals per time after the dose were used except the blank controls. Each subject was tested only once. All experiments respected the Guidelines of the European Union Council (86/609/EU) and followed the instructions of the National Committee for the Care and Use of Laboratory Animals.

Drugs and chemicals

Behavioral experiments Mescaline.HCl (Sigma Aldrich) was dissolved in a physiological saline solution. The drug or vehicle was administered subcutaneously (s.c.) in a volume of 2 ml/kg.

Toxicological analysis Mescaline.HCl and mescaline-D9. HCl standards for calibration and method validation were supplied by Sigma Aldrich and Cambridge Isotope Laboratories. The reagents used for these purposes were of general analytical grade purity.

Experiment 1: Study of disposition in blood and brain

For this kinetic study, a single bolus dose of mescaline 20 mg/kg was injected into the rats, and subsequently, animals were killed after 30, 60, 120, and 480 min. For control purposes, physiological saline solution was injected as well. Separated sera and whole brains were kept at −20°C until toxicological analyses were performed.

Sample preparation for GC-MS

Serum Serum (0.5 ml) was mixed with 0.5 ml 0.1 M phosphate pH 6 and 200 ng deuterated mescaline (internal standard, IS), and analytes were isolated using SPEC-DAU discs. The eluates were evaporated to dryness at 40°C and then derivatized with 200 μl of an acetic acid anhydride/pyridine (10/1, *v*/*v*) mixture at 60°C for 30 min, then evaporated again, transferred into 100 μl ethylacetate, and subsequently, 1 μl was injected for gas chromatography–mass spectrometry (GC-MS) analysis.

Brain tissue Whole brain tissue (1.3 g) with 500 ng deuterated mescaline (IS) were homogenized with 5 ml methanol and submitted to sonification for 15 min. After centrifugation (5 min at 4000 rpm), 2 ml supernatant were separated, evaporated to dryness, and dissolved in 100 μl methanol and 1 ml 0.1 M phosphate pH 6 for isolation on SPEC-DAU discs and acetylation as described for the serum.

GC-MS conditions

A HP 6890-5973 (Agilent, Waldbronn, Germany) instrument equipped with an autosampler, splitless injector, HP5-MS 30 m×0.25 mm×0.25 μm capillary, and 1 ml/min constant He flow was used. The oven temperature was programmed starting from 85°C, held for 2 min, then 30°C/min up to 150°C, then 15°C/min up to 250°C and then held for 10 min. The injector and transfer line were held at 250°C. Ionization was carried out in electron impact at 70 eV. SIM mode was used with monitoring of m/*z* 181 *194* 253 for mescaline and 190 *203* 262 for the deuterated internal standard. The italicized ions were used for quantification.

Toxicological method

The GC-MS toxicological methods were developed and validated according to the international standards, e.g., Lindner and Wainer (1998); Penders and Verstraete (2006); Peters et al. (2007), to determine the mescaline concentrations in rat serum and brain tissue samples under the operating conditions described above. Blank rat sera and brain tissue were used in the method validation process and for calibration purposes. For quantitation, the internal standard method was used. The calibration curves were constructed using linear regression analysis based on the ratio of mescaline peak area to the internal standard.

Experiment 2: Behavioral experiments

Study design—PPI

All of the rats were initially tested in a short session (a 5-min acclimatization period plus five single pulses) to determine the drug-free baseline startle magnitude 2 days before the experiment. On the experiment day, mescaline (10, 20, and 100 mg/kg) or saline was administered 15 or 60 min before the start of the testing session.

All testing was performed in the startle chamber (SRLAB, San Diego Instruments, California, USA). A high-frequency loudspeaker inside the chamber produced both a background noise of 62 dB and the acoustic stimulus 120 dB. The experiment design was adopted from Bubenikova et al. (2005). After the acclimatization period (5 min), the test began with five initial startle stimuli (120 dB) followed by four different trial types presented in a pseudo-random order: (1) single pulse: 120 dB broadband burst, 20 ms duration; (2) prepulse: 13 dB, 20 ms duration above the background noise, presented 100 ms before the onset of the pulse alone; (3) prepulse alone: 13 dB, 20 ms duration above the background noise; (4) no stimulus. Five presentations of each trial type were given with an interstimulus interval of about 30 s. The PPI was expressed as a percentage of PPI [100−(mean response for the prepulse–pulse trials/startle response for the single-pulse trials)×100]. The four single-pulse trials at the beginning of the test session were not included in the calculation of the PPI values. Animals having an average startle value lower than 10 were excluded from the PPI calculation and were marked as being non-responsive. The number of animals removed did not differ significantly among all of the treatment groups.

Study design—open field

Locomotor activity (trajectory length) and its spatial characteristics (thigmotaxis and time spent in the center) were registered and analyzed by an automatic video tracking system for recording behavioral activities (EthoVision Color Pro v. 3.1.1, Noldus, Netherlands) in a novel environment. A square black plastic box arena (68×68×30 cm) was placed in a soundproof and equally lit room. Two groups of rats for each dose of mescaline were evaluated. Each rat was placed into the center of the arena 15 or 60 min, respectively, after drug administration (mescaline 10, 20, and 100 mg/kg or saline), and locomotor activity was registered for another 30 min. The EthoVision program was also used to calculate locomotor data in 5-min time intervals. To describe the spatial characteristics of the movement in the open field (thigmotaxis and time spent in the center of the arena), the arena was divided virtually by the EthoVision program into 5×5 identical square zones, with 16 being located on the periphery and 9 centrally. Initially, a total number of appearances of the animal in each zone (frequency; *f*) and time spent in each zone ($t_{1–16}$) were calculated by the program. The thigmotaxis was calculated as $i = f_{peripheral\,zones} / f_{all\,zones}$. Thus, the thigmotaxis (*i*) is a relative number which varies from 0–1 and indicates a probability of appearance in any of the peripheral zones within the arena. As a complementary measure, time spent in the center of the arena (T_{center}) was analyzed, equaling the summation of time spent in the nine central zones ($\Sigma t_{1–9}$).

Statistical analysis

Statistical analysis of all behavioral data was performed using the program SigmaStat v.3.0. Data from all experiments were collected and statistically evaluated by one-way analyses of variance. When appropriate, comparisons between treatment groups and controls were conducted using the Bonferroni post hoc test.

Results

GC-MS method validation parameters

In our study, the deuterated internal standard both in serum and in the brain assured that the method for the determination of mescaline was selective and all of the requirements for identification and quantification were fulfilled (Lindner and Wainer 1998; Peters et al. 2007). The serum method was linear in the range of 20–2000 ng/ml, with a regression coefficient of 0.9955 based on spiked blank rat sera in duplicate (Fig. 1). The lower limit of quantification (LLOQ) was set to 20 ng/ml. Repeatability in a day was tested (n=6) with the results ±1.7% (c=2,000 ng/ml) or ±7.5% (c=20 ng/ml). Accuracy was estimated as +11% (c=500 ng/ml). The detection limit (LOD) was estimated from a separate calibration in a low concentration range and set to 5 ng/ml (S/N>3).

The brain tissue method was linear in the range of 20–1000 ng/g, with a regression coefficient of 0.9994 based on spiked blank brain tissue in duplicate (Fig. 1). The LLOQ was set to 20 ng/g. Repeatability in a day was tested (n=6) with the results ±1.8% (c=1,000 ng/ml) or ±13% (c=20 ng/ml). Accuracy was estimated as +12% (c=100 ng/ml). The LOD in the brain was estimated from a separate calibration in a low concentration range and set to 5 ng/g (S/N>3). Typical ion chromatograms of serum or brain acetylated extracts of assayed rat samples with mass spectra related to mescaline and internal standard are illustrated in Fig. 2a and b.

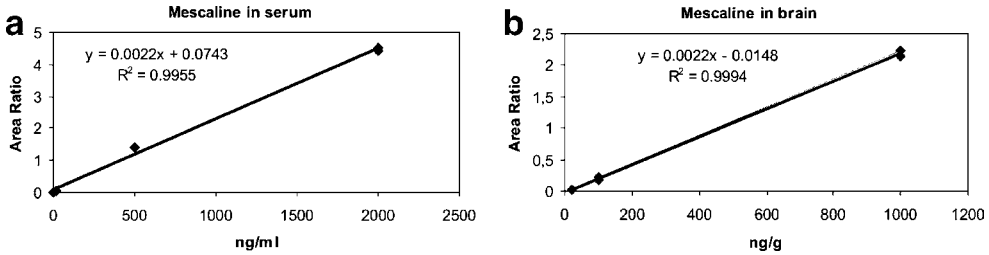


Fig. 1 Linearity of GC-MS method for mescaline determination in serum (**a**) and brain tissue (**b**)

Experiment 1: Time profile of serum and brain levels of mescaline after s.c. dose

The determined levels of mescaline in blood serum and brain tissue of individual rats killed after 30, 60, 120, or 480 min after the subcutaneous dose are summarized in Table 1. The mean values (n=6) are presented in the Fig. 3a where the time profile and the concentration maxima of mescaline both in serum and the brain are apparent with a clear delay of approximately 30 min for the brain related to serum. The brain levels remained significantly lower related to serum levels up to 2 h after drug application. On the basis of our experiments, the mescaline halftime in rat serum can be roughly estimated from the semilogarithmic plot presented in Fig. 3b, and it appears to be close to 1 h.

Experiment 2: Behavioral experiments

PPI and startle Startle reaction did not differ from the controls when tested 15 min after application [$F(3,51)$= 0.85, p=0.47]; however, at 60 min, mescaline significantly decreased the startle magnitude [$F(3,51)$=2.8, p=0.05] which was apparent for mescaline 100 mg/kg (p<0.05) but not for any other dose (Table 2). The PPI was not attenuated 15 min after application [$F(3,43)$=1.45, p=0.24]; however, there was a significant disrupting effect of all mescaline treatments at 60 min [$F(3,51)$=4.2, p=0.01]. Each mescaline treatment differed from the control group at p<0.05 (Fig. 4a,b).

Locomotion Total locomotion did not differ from the controls when tested 15 min after application [$F(3,39)$= 1.79, p=0.67; Fig. 5a]. However, there was a significant effect of mescaline treatment at 60 min [$F(3,39)$=34.18, p<0.001]; mescaline 100 mg/kg produced marked hyperlocomotion (p<0.001) compared to the control group (Fig. 5b).

After calculating trajectory length in 5-min intervals during the testing period, the significance was determined in both time schedules. In the first schedule, when mescaline was administered 15 min before testing, there were significant differences during the first 5-min interval [F(3,39)=3.58, p<0.05] where mescaline 100 mg/kg induced hypolocomotion (p<0.01) and during the second 5-min interval [$F(3,39)$=3.52, p<0.05] where mescaline 20 and 100 mg/kg induced hypolocomotion (p<0.05 in both

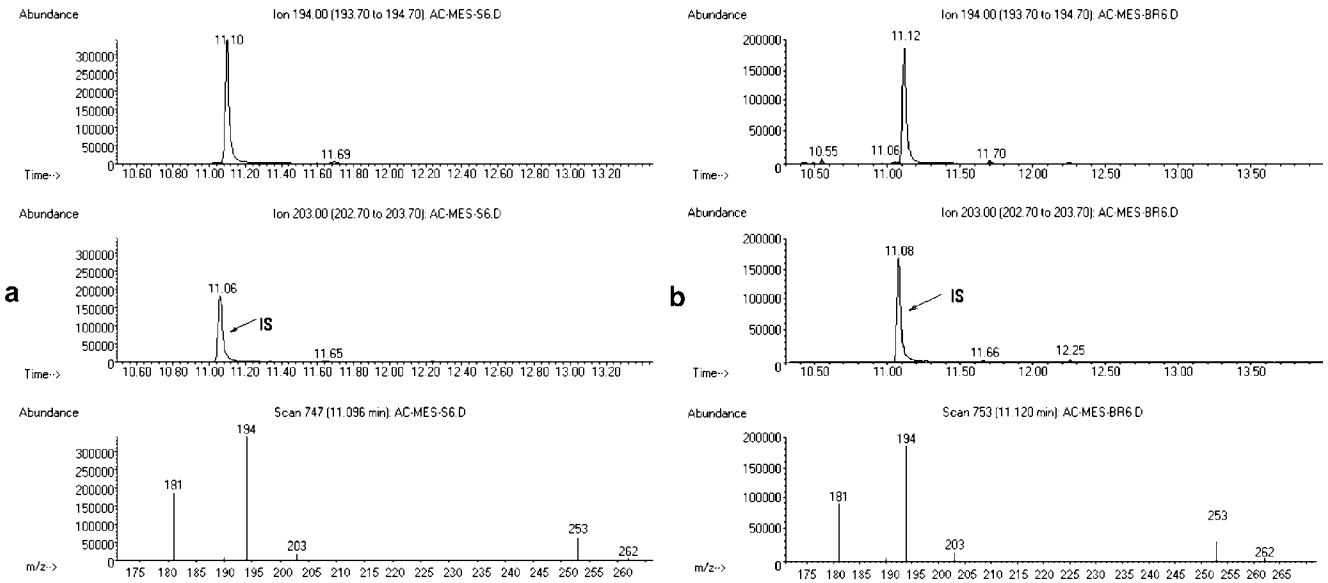


Fig. 2 **a** Typical ion chromatograms of acetylated serum extract of an assayed rat sample with mass spectra related to mescaline and the deuterated IS. **b** Typical ion chromatograms of acetylated brain extract of an assayed rat sample with mass spectra related to mescaline and the deuterated IS

Table 1 Mescaline disposition in individual rats in time after a single s.c. dose (20 mg/kg)

Rat no.	Time (min)	Serum (ng/ml)	Brain (ng/g)	Ratio serum/brain
1	30	1578	258	6.1
2	30	1939	346	5.6
3	30	1890	357	5.3
4	30	1171	349	3.3
5	30	1354	450	3.1
6	30	2007	458	4.4
7	60	1583	601	2.6
8	60	1078	547	2.0
9	60	393	348	1.1
10	60	1207	543	2.2
11	60	1671	622	2.7
12	60	1548	418	3.7
13	120	743	456	1.6
14	120	503	491	1.0
15	120	419	326	1.3
16	120	190	333	0.6
17	120	169	383	0.4
18	120	834	467	1.8
19	480	n.d.	qual.	
20	480	n.d.	n.d.	
21	480	n.d.	n.d.	
22	480	qual.	qual.	
33	480	n.d.	qual.	
44	480	n.d.	qual.	

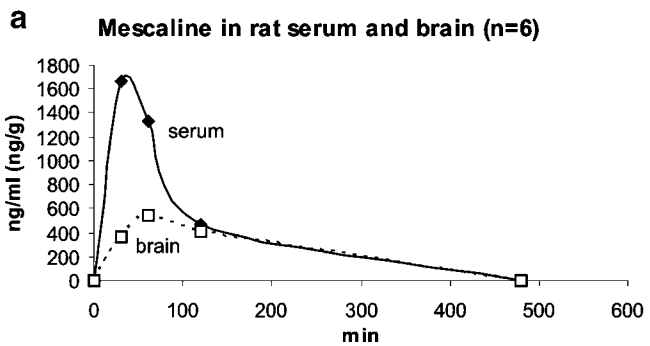
n.d. not detected, below LOD (5 ng/ml or ng/g)
qual. detected below LLOQ (20 ng/ml or ng/g)

cases). Other 5-min intervals revealed no significant differences (Fig. 6a). When the testing was performed 60 min after the administration, there were significant differences during the first 5-min interval [$F(3,39)=26.87$, $p<0.001$] where mescaline 10 and 20 mg/kg induced hypolocomotion ($p<0.001$ and $p<0.01$) and during all of the other 5-min intervals [$F(3,39)=19.13$ (for 5–10 min), 37.09 (for 10–15 min), 28.53 (for 15–20 min), 21.66 (for 20–25 min) and 23.29 (for 25–30 min), $p<0.001$ in all intervals] where mescaline 100 mg/kg induced hyperlocomotion ($p<0.001$; Fig. 6b).

Thigmotaxis (i) and time spent in the center (T_{center}) Mescaline had no effect on thigmotaxis either 15 or 60 min after application. Time spent in the center was not attenuated at 15 min post-application, but there was a significant effect of mescaline treatment at 60 min [$F(3,39)=3.051$, $p<0.05$]. However, post hoc analysis did not reveal any significant differences among treatment groups.

Discussion

After the single subcutaneous injection of mescaline.HCl 20 mg/kg, concentrations in serum quickly increased to peak values at 30 min, with a subsequent rapid decrease at 60 min and a slower decrease to 120 min. However, the peak brain concentrations of mescaline developed much slower compared to serum, slightly increasing to a peak at 60 min. At 120 min post-injection, the brain concentrations became close to those in serum. As described previously, mescaline crosses the blood–brain barrier poorly due to its polar molecular characteristics (Spinella 2001; Laing and Siegel 2003). This was clearly confirmed by our results, as the highest brain concentrations of mescaline were about one third of those ascertained in serum. Regarding its pharmacokinetics, the effects of mescaline in the behavioral experiments were also more pronounced when animals were tested 60 min after administration when maximum levels in the brain were achieved. Thus, as expected, our findings are in accordance with the described delayed onset of mescaline behavioral effects and duration of action. However, our results with experimental rats indicate different—faster pharmacokinetics as well as behavioral action compared to humans (Foltz et al. 1980; Silva et al. 1960; Hermle et al. 1992; Charalampous and Kinross-Wright 1963; Charalampous et al. 1966).



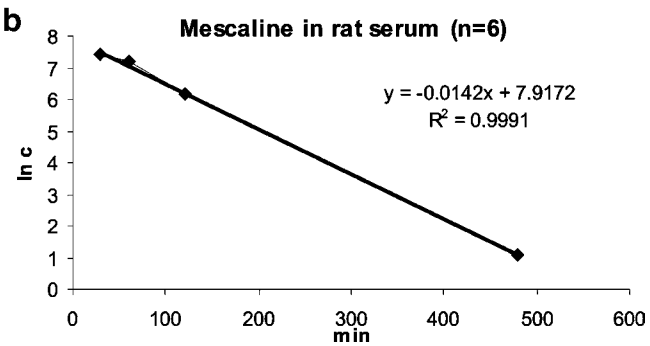


Fig. 3 Mescaline in rat serum and brain (mean, $n=6$) after a single s.c. dose of mescaline.HCl (20 mg/kg) vs time. **a** The time course of mean mescaline levels in serum and brain of experimental rats ($n=6$) after a single s.c. dose (20 mg/kg); **b** the semilogarithmic plot of rat serum levels c vs time (mean, $n=6$) after a single s.c. dose of mescaline.HCl (20 mg/kg)

Table 2 Startle reaction

	Time of administration (min)	Mescaline dose			
		0 mg/kg	10 mg/kg	20 mg/kg	100 mg/kg
Mean of startle amplitude (±SEM)	15	66.21 (11.89)	85.20 (11.42)	82.62 (16.14)	60.86 (10.5)
	60	64.35 (10.39)	43.35 (5.33)	46.15 (6.83)	37.04 (2.95)*

Acoustic startle reaction at 15 min and 60 min after the mescaline (10, 20, and 100 mg/kg) administration. Mescaline 100 mg/kg at 60 min after the administration produced significant disruption of acoustic startle.
*Indicates $P<0.05$ from the control group

We found that mescaline produced a biphasic effect on locomotion. The hypolocomotor effect was apparent mainly during the initial two 5-min intervals after the animal was introduced into the novel environment in both time schemes for the two lower doses of mescaline. The high dose of mescaline (100 mg/kg) tested 60 min after application led to a pronounced overall hyperlocomotion that continued during all 5-min periods. When animals were tested 15 min post-injection (when the brain concentration of the drug was low), the hypolocomotor effect during the initial phase was present similarly to the two other doses. With the exception of the highest dose, mescaline showed similar effects on locomotion as most other hallucinogens in comparable testing procedures described by others, e.g.. Palenicek et al.(2006); Krebs-Thomson et al. (1998); Geyer et al. (1979); Krebs-Thomson et al. (1998); Krebs-Thomson and Geyer (1996). The observed initial hypolocomotion may be a result of motor impairments produced by the drug such as ataxia. The latter mentioned effect has been described by Sykes (1986) after treatment with 25 mg/kg of mescaline using two different methods. The inhibition of ambulation by mescaline was also described by others (Silva and Calil 1975) as well as the biphasic—depressant followed by stimulant—effect on other performance in rats (Sykes 1986; Smythies and Sykes 1964; Bourn et al. 1978; Geyer et al. 1979). A biphasic effect in a hole-board test was also described for other hallucinogenic drugs like DMT (*N*,*N*-dimethyltryptamine), psilocin, DOM, or DOET (2,5-dimethoxy-4-ethylamphetamine; Geyer et al. 1979). As the behavior was evaluated continuously in these experiments, the biphasic effect of LSD and other psychedelics was independent of the pretesting interval, which is not the case in our study. On the other hand, the effects of mescaline in our study were so robust that we may speculate that the effect would be present even if we would monitor the behavior continuously. The hallucinogenic effects of psychedelics are thought to be mediated primarily via serotonin 5-HT_{2A} receptor agonism (Nichols 2004). However, most phenethylamine hallucinogens also bind with similar potency to serotonin 5-HT_{2C} receptors (Nichols 2004). Both of these receptors are also involved in the modulation of dopaminergic neurotransmission, and it is likely that they control in the opposite way the release of dopamine. As the serotonin 5-HT_{2A} receptor is thought to control phasic release of dopamine, the $5HT_{2C}$ receptor is involved in the control of tonic dopamine release (Barnes and Sharp 1999; Bankson and Cunningham 2001). Taking into account that dopamine is a key neurotransmitter in controlling motor behavior, it is plausible that the observed effects are mediated indirectly via activation/inhibition of dopaminergic systems. In our previous study, we found that the administration of the selective serotonin 5-HT_{2C} antagonist

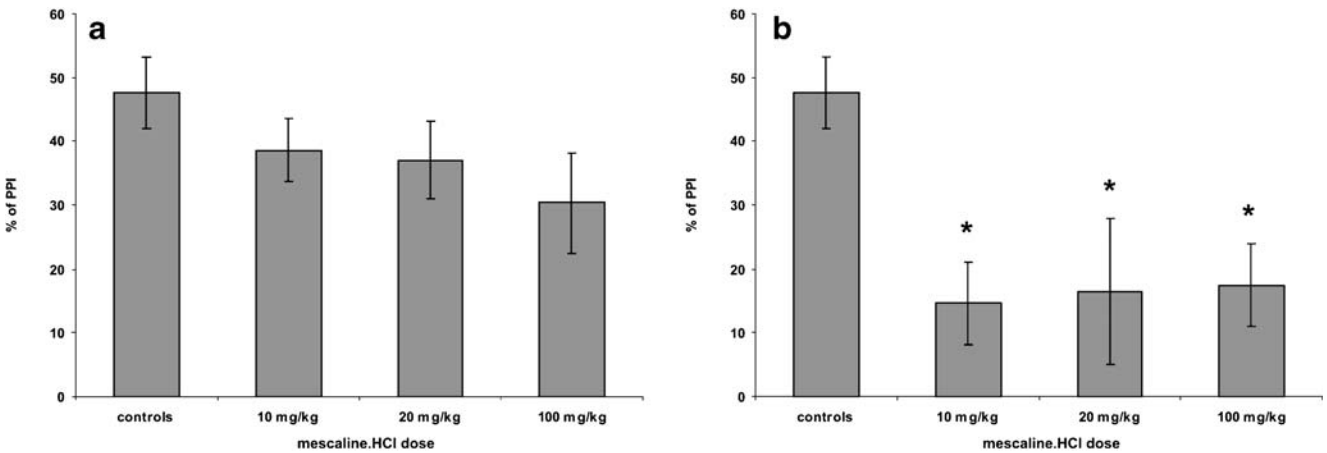


Fig. 4 PPI. PPI 15 min (**a**) and 60 min (**b**) after mescaline (10, 20, and 100 mg/kg) administration. All mescaline treatments at 60 min after the administration produced significant disruption of PPI (*$P<0.05$ from the control group)

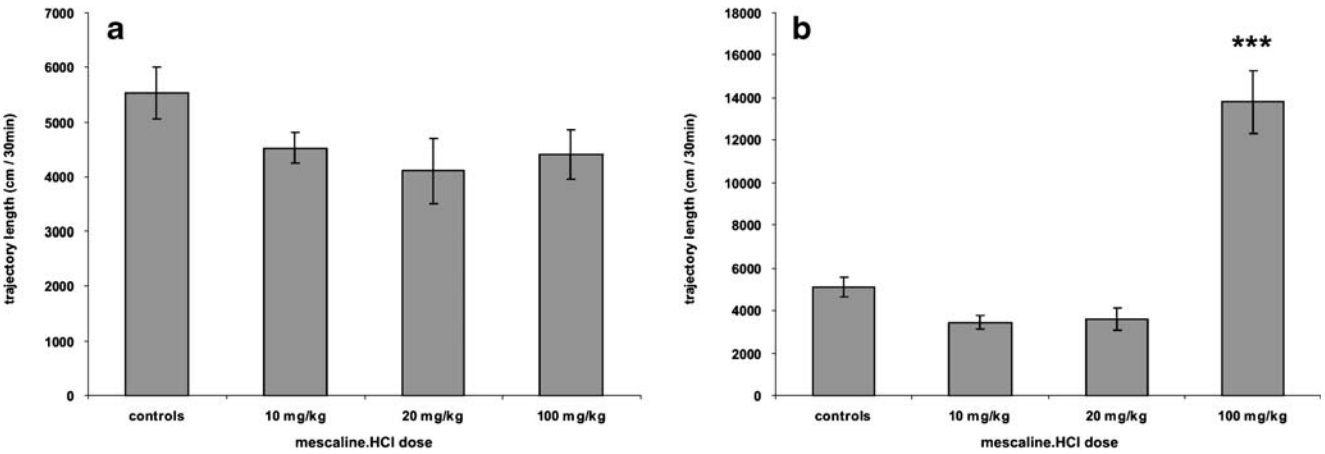


Fig. 5 Total locomotion within 30 min. Locomotion 15 min (**a**) and 60 min (**b**) after mescaline (10, 20, and 100 mg/kg) administration. Mescaline 100 mg/kg 60 min after the administration produced significant hyperlocomotion (***$P<0.001$ from the control group)

SB242084 prevented hypolocomotor effects induced by psilocin (Palenicek et al. 2006) and 2C-B (4-bromo-2,5-dimethoxyphenethylamine; unpublished data). Thus, the hypolocomotor effects of mescaline could similarly be a result of an activated serotonin 5-HT_{2C} receptor. Moreover, mescaline seems to have slightly higher affinity on the serotonin 5-HT_{2C} receptor over the 5-HT_{2A} receptor (Monte et al. 1997). Congruently, antagonists of this receptor increase the release of dopamine in microdialysis experiments, suggesting that serotonin 5-HT_{2C} receptors exert a tonic inhibitory influence on mesocortical/mesolimbic dopaminergic projections (Barnes and Sharp 1999). On the other hand, independently of the pretesting interval, Mittman et al. also described a biphasic effect of LSD on locomotor activity, with initial hypolocomotion followed by a subsequent increase in locomotion. The increase in locomotion produced by LSD has been successfully blocked by the serotonin 5-HT_{2A} receptor antagonist ritanserin (Mittman and Geyer 1991). Similarly, Yamamoto and Ueki (1975) have observed a biphasic effect of DOM on locomotion which was present in high doses but not in low doses. It is, thus, probable that mescaline during the onset of action as well as at 60 min post-drug administration affects serotonin 5-HT_{2C} receptors which then are responsible for the observed hypolocomotor effect or ataxia. Nonetheless, the highest dose could stimulate more other serotonin receptors, especially 5-HT_{2A} and 5-HT_{1A}, and could possibly also have direct dopaminergic or noradrenergic action similar to LSD (Trulson et al. 1983; Ahn and Makman 1979; Mittman and Geyer 1991; Laing and Siegel 2003). Taken together, the high dose of mescaline also may lead to dopaminergic stimulation. In such case, stimulation of serotonin 5-HT_{2A} receptors will have a facilitator role on the dopamine release, and this could result in the observed hyperlocomotion. This phenomenon is also in accordance with Fink et al. (1979) who observed strong potentiation of amphetamine and apomorphine hyperlocomotion by low doses of LSD, mescaline,

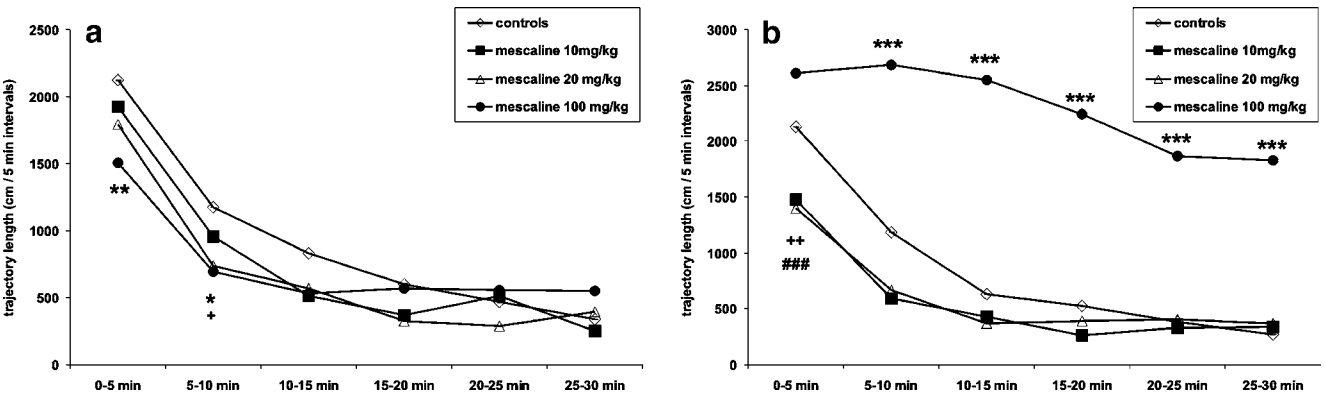


Fig. 6 Total locomotion by 5-min intervals. Locomotion 15 min (**a**) and 60 min (**b**) after the mescaline (10, 20, and 100 mg/kg) administration. Mescaline 10 and 20 mg/kg inconsistently produced hypolocomotion during the first two 5-min intervals in both testing paradigms; mescaline 100 mg/kg 15 min after the administration produced hypolocomotion during the first two 5-min intervals; 60 min after the administration, it produced significant hyperlocomotion in all intervals (differences from the control group: *indicates Mescaline 100 mg/kg $P<0.05$, **indicates mescaline 100 mg/kg $P<0.01$, ***indicates mescaline 100 mg/kg $P<0.001$, +indicates mescaline 20 mg/kg $P<0.05$, ++indicates mescaline 20 mg/kg $P<0.01$, ###indicates mescaline 10 mg/kg $P<0.001$)

and DMT. Similarly, activation of postsynaptic serotonin 5-HT_{1A} receptors leads to hyperlocomotion (Carey et al. 2004) as well as to an increase in dopaminergic and noradrenergic activity (Chen and Reith 1995; Rollema et al. 2000; Gobert et al. 1998; Lejeune and Millan 2000).

Kaur and Ahlenius (1997) described thigmotaxis of rats induced by the hallucinogen DOI. However, we did not observe any significant effect of mescaline in any dose used on the thigmotaxis. On the other hand, there was a significant effect on time spent in the center 1 h after drug administration without a significant difference between individual groups. Mescaline induced a slight decrease at 10 and 20 mg/kg and subsequent increase at 100 mg/kg in time spent in the center, with differences between mescaline 10 and 100 mg/kg almost reaching significance. This could be again the consequence of hyperlocomotion produced by 100 mg/kg of mescaline.

The startle reaction to acoustic stimuli was not altered in our setting except for the highest dose at 60 min post-application. Unlike others who have reported an increase in startle reaction (Davis 1987; Geyer et al. 1978), we observed a decrease in startle produced by mescaline 100 mg/kg at 60 min post-treatment. This could reflect the robust motor changes produced by the drug. A similar trend was present for two other doses at this time. However, at 15 min post-injection, an insignificant increase in animals treated with mescaline 10 and 20 mg/kg is apparent. The prepulse inhibition of acoustic startle as a matter of sensorimotor information processing remained unaffected by any mescaline treatment during the testing at 15 min post-injection; however, at 60 min, all doses used significantly disrupted prepulse inhibition. The disrupting effect of mescaline on PPI is in accordance with other studies with hallucinogenic agents which have comparable effects, e.g., Ouagazzal et al. (2001); Johansson et al. (1995); Sipes and Geyer (1995b); Krebs-Thomson et al. (2006); Vollenweider and Geyer (2001). In the recent paper of Ouagazzal et al. (2001), the authors have described disruption of PPI by LSD which was restored by selective antagonist of serotonin 5-HT_{2A} receptors MDL100907, but not by selective antagonist of serotonin 5-HT_{2C} receptors SB242084. Thus, it would not be surprising that the same mechanisms would be involved in the action of mescaline.

However, it is difficult to compare our results with those of other authors, as often, a different rat strain or gender was used. Furthermore, the i.p. route of administration was most frequent. Sykes (1986) described that mescaline produced motor impairment in female rats from 30–40 min after i.p. administration. Similarly, the tactile startle was attenuated at 30 min post i.p. administration of mescaline 10 and 20 mg/kg (Geyer et al. 1978). On the other hand, a 0- to 20-min pretest interval after either i.p. or s.c. administration was used by others in various tests, e.g., Wing et al. (1990); Sykes (1986); Harris et al. (1978); Gorelick and Bridger (1977); Davis (1987); Geyer et al. (1979); Silva and Calil (1975). Interestingly, in previously published drug discrimination studies, animals were able to discriminate mescaline 5 and 15 min after relatively low doses of mescaline (9.9 and 15 mg/kg; Browne et al. 1974; Hirschhorn and Winter 1971). This is intriguing, as in our study, the maximum behavioral effects were present 60 min after administration. However, again, in both latter-mentioned experiments, i.p. administration routes and different rat strains and/or female rats were used. On the other hand, in the work done by Browne et al. (1974), rats were also able to discriminate the drug from saline 30 and 45 min after i.p. application, followed by a continuous decrease in discrimination up to 360 min. This is much closer to our observations. As we have also found some insignificant trends in mescaline-altered behavior 15 min after administration with the lower doses (the only significant effect was mescaline 20 mg/kg for locomotion during the interval 20–25 min after administration), this indicates that some behavioral effects can also be present during the onset of the drug action. Interestingly, in a drug discrimination study with DOM, a drug structurally closely related to mescaline, the most efficacious pretreatment time has been found to be 75 min instead of 15 min after drug administration compared to indolealkylamine hallucinogen LSD (Fiorella et al. 1995). Thus, in mescaline discrimination studies, it is possible that rats are able to discriminate the onset of the action of the drug. The decreased response of rats from 45 min post-administration reported by Browne et al. (1974) may also reflect decreased motor abilities of animals (hypolocomotion, ataxia) and/or the decreased capability to adequately operate with the discrimination task due to the disruption of sensorimotor processing (and suspiciously induced alterations in perception and cognitive functions with respect to the hallucinogenic potency of the drug).

It is important to note that apart from the experimental protocol, we have observed that approximately 50% of animals receiving 100 mg/kg died within 12 h post-injection. This is in accordance with Hardman et al. (1973) who described LD50 in Sprague–Dawley rats to be 132 mg/kg after i.p injection, but in contrast with the findings of Speck (1957) who described in male albino rat the LD50 to be 370 mg/kg after i.p. administration and with Davis et al. (1978) who described LD50 in male Sprague–Dawley rats to be 270 mg/kg i.p.. Speck (1957), in his study, described that flexor convulsions and respiratory arrest were the terminal events of animals; Davis et al. (1978) described that rats were very inactive, hypoactive, they showed repetitive swimming-like movements, and that they had muscular weakness and ataxia. In our setting, we observed that animals elicited a flat body posture along with hyperlocomotion and almost no rearing. Finally, they stopped

moving, became unresponsive, and respiratory arrest followed. With respect to these facts, we cannot eliminate that the observed effects of the highest dose of mescaline are not partly a consequence of its toxicity.

Our study has described acute behavioral effects of mescaline in two different testing paradigms. It indicates that maximum effects of mescaline in male Wistar rats appear at 60 min after subcutaneous injection, and these findings correlate with the brain tissue peak concentrations. This is the first study to our knowledge which has described the temporal brain profile of mescaline related to its behavioral effects. The importance of our data is mainly in the evidence that the maximum psychoactive or behavioral effects of mescaline directly correlate with its pharmacokinetics. It is important to note that in many previous studies, mescaline action was often not tested with the appropriate timing, when it has its maximum effects, indicating that these studies have described only the approximate psychotropic potency of this drug. Another important consequence of our study is that it could help us recognize the effects and potential risks associated with the abuse of other methoxylated phenylalkylamines that appear more frequently on the illicit market. Some of them have been reported to have comparable effects to mescaline in humans as well as a delayed onset of action, e.g., TMA (3,4,5-trimethoxyamphetamine), TMA-2 (2,4,5-trimethoxyamphetamine), 2C-B, 2C-I (4-iodo-2, 5-dimethoxyphenethylamine), or DOB (4-bromo-2, 5-dimethoxyphetamine; EMCDDA 2004b; Foltz et al. 1980; Balikova 2005; EMCDDA 2004a; EMCDDA Joint Action on NSD 2005; French Identification Ssystem for Synthetic Drugs of OFDT (SINTES) 2003; Giroud et al. 1998; National Drug Intelligence Center 2001; Owen 2005; http://www.erowid.org). Thus, studies that incorporate pharmacokinetics together with behavioral testing of substances of interest are of great importance, and our current study can serve as a model for further research.

Acknowledgments This work is supported by projects IGA MHCR NR8785-3, IGA MHCR NR8332-3 and MEYS CR 1M0517. We thank Craig Hampson BSc (Hons) for helpful comments and language correction.

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