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Development of Tolerance to the Antinociceptive Effect of Mescaline Intraventricularly Administered to Rabbits

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Abstract. Some effects of intraventricular injection of mescaline are examined in conscious rabbits. By means of electrical stimulation of the tooth pulp it is shown that an acute treatment with 70, 100, 150 µg/kg of mescaline elicits analgesia, the intensity of which is dose-dependent: with daily administration of 100 µg/kg for 5 days a complete tolerance develops to the antinociceptive effect. A tolerance also develops to the behavioral effects of mescaline after repeated administrations, with the exception of the stuporous state, a symptom which, on the contrary, is accentuated as the treatment proceeds. An EEG arousal is induced in the rabbit by acutely administered mescaline; the chronic treatment (100 µg/kg) makes the return of voltage to original levels progressively slower.

Finally, the confrontation of certain of the mescaline-induced effects with those of morphine suggests some biochemical and neural patterns common to the 2 drugs.

Key words: Mescaline – Nociception – EEG – Gross behavior.

The hallucinogens have been thoroughly investigated for their effects on the central nervous system but so far only a few reports are available on the development of a tolerance to these effects. On the other hand, it is evident that if patterns of tolerance could be clearly delineated, the mechanisms underlying the action on the CNS of these drugs would be easier to understand. As regards mescaline, in particular, a tolerance was observed in rats as evaluated through their gross behavioral and rope-climbing performances (Freedman et al., 1958), whereas the reduction of mescaline-induced bradycardia after repeated administrations is still a matter of controversy (Speck, 1957; Lehr and Werner, 1970).

Since a decreased sensitivity to pain has been described for mescaline in some species (Schwartz et al., 1956), we have undertaken the present investigation in order to ascertain whether a tolerance develops to the antinociceptive effect in the rabbit after repeated intraventricular administrations. Observations are also reported here concerning the rabbit's behavior and additional data are given in the attempt to correlate the analgesic and behavioral responses with the electrical activity of the rabbit brain after acute and chronic treatment with mescaline.

MATERIALS AND METHODS

The experiments were performed in male adult rabbits weighing between 2.5 – 3 kg. Under nembutal anesthesia stainless steel electrodes were implanted in their brains by standard stereotaxic techniques using the coordinates of Monnier and Gangloff (1968), for the rabbit. The electrode sites were as follows: nucleus medialis dorsalis thalami, formatio hippocampalis ventralis, formatio reticularis mesencephali, cortex motoris, and nucleus caudatus. A stainless steel screw, fixed in the nasal bone, served as ground reference. The electrodes were secured with dental cement (Palacos).

The animals were placed in shielded cages and their brain potentials were recorded on an 8-channel electroencephalograph (Mod. Neuro 20 Battaglia-Rangoni) for 40 min before the administration of the drug and for 120 min after. One lead (n. caudatus) was analyzed by means of a voltage integrator in order to have a quantitative evaluation of the electrogenesis.

The licking reaction elicited by electrical stimulation of the pulp of the upper incisors was used as a nociceptive reaction (Hoffmeister, 1968). A hole of about 1 mm in diameter extending almost to the pulp was drilled in a central position of the incisors and two gold stimulation electrodes were secured inside the holes with dental cement, leaving the tips uncovered.

These electrodes were connected to a square-wave Palmer stimulator (C.V.P. model). In each stimulation schedule the frequency, pulse width, and duration of the stimulus remained constant at 5 Hz, 5 ms, and 2 s respectively: only voltage varied until the licking reaction was elicited: the pain threshold was verified every 10 min for 120 min and expressed in volts.

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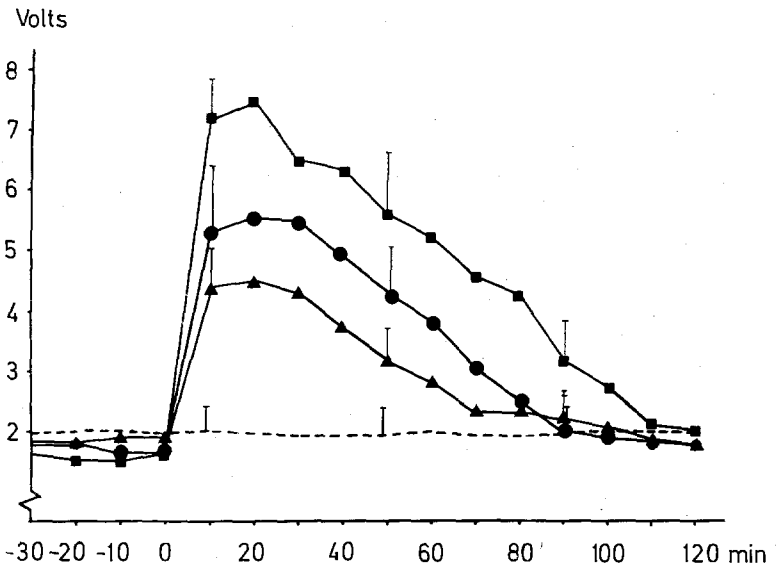

Fig. 1
Pain threshold (voltage) to electrical stimulation of tooth pulp in rabbits, given intraventricularly either saline (----) or mescaline: 70 μg/kg (▲——▲); 100 μg/kg (●——●); 150 μg/kg (■——■). Mean values of 8 animals with some standard errors

A stainless cannula was chronically implanted into the anterior horn of the right lateral ventricle for the ventricular application of the drug (Feldberg and Sherwood, 1953). Mescaline, H_2SO_4 (Merck), was dissolved in saline solution and injected, in acute experiments, in doses of 70, 100, 150 μg/kg in a constant volume of 50 μl.

For chronic observations a dose of 100 μg/kg of mescaline was chosen and its intraventricular administration was repeated for 5 days, every day, at the same hour.

Control animals received an equal volume of saline.

The cannula placement was verified by means of an intraventricular dye injection at the end of the experiments; electrolitic lesions were also made in order to confirm the electrode positions.

The statistical procedures adopted were those indicated by Steel and Torrie (1960).

RESULTS

Antinociceptive Effect after Acute and Chronic Mescaline Administration. In Figure 1 the mean voltages are reported, with some representative standard errors, required to provoke the licking reaction in rabbits. While saline is ineffective, mescaline, for all the doses employed, enhances the threshold to the painful stimulus. The antinociceptive effect has a rapid onset, reaches quickly its maximum, and then progressively declines until it disappears by the end of the second hour of observations A regression line of mescaline's analgesic effect on the log of the administered dose may be drawn when analgesia is calculated in terms of whole activity area (Fig. 2). The effect of 100 μg/kg of mescaline on the nociceptive stimulus when injected daily into the brain ventricle for 5 days is shown in Figure 3; the pain threshold declines rapidly as the administration proceeds in time and an almost complete tolerance to the antinociceptive effect of 100 μg/kg of mescaline develops by the 5th day of treatment.

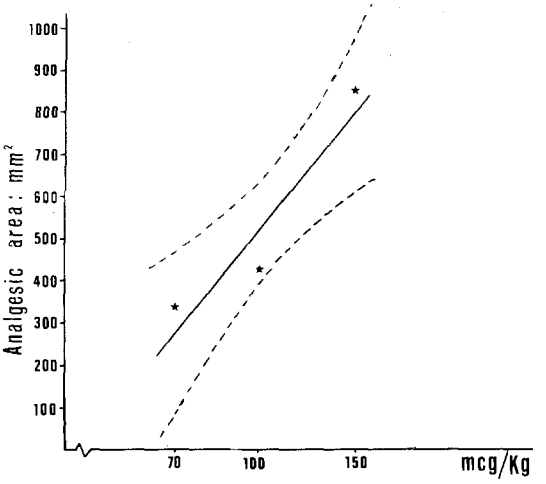

Fig. 2. Regression line of analgesic activity of mescaline (plotted in terms of total analgesic area) on log of drug doses. Regression equation: $Y = -2632.37 + 1577.05\,X$

Observation of Behavior. The most marked and constant effect produced by the intracerebroventricular injection of every single dose of mescaline (from 70 to 150 μg/kg) consisted in a stuporous condition, which set in progressively beginning at the 30th–60th min after administration. The rabbit remained in the same position for unusually long periods of time. Initial excitement and running movements, lasting a short time, preceded this stuporous phase. A few animals, treated with the highest dose of mescaline, displayed a catatonic-like state with the tone of the neck muscles highly increased. Most of them exhibited hind leg relaxation, chewing movements, and also salivation,

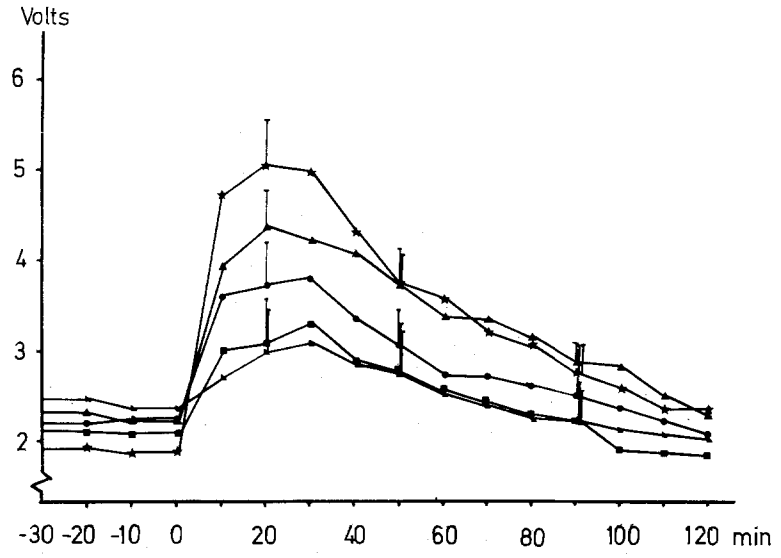

Fig. 3
Progressive decrease in analgesic effect of mescaline (100 μg/kg) given intraventricularly for 5 days: ✕——✕ 1st day; ▲——▲ 2nd day; ●——● 3rd day; ■——■ 4th day; ◣——◣ 5th day. Mean values of 8 animals with some standard errors

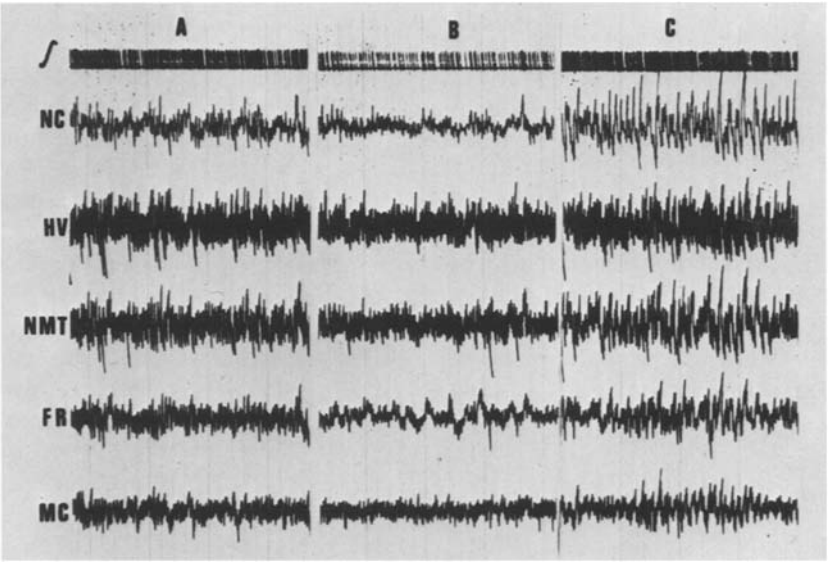

Fig. 4
Effect of single intraventricular injection of mescaline (100 μg/kg) on EEG activity of rabbit. A = Control; B = 10 min after mescaline; C = 60 min after mescaline. Voltage decreased and then increased in all leads. Calibration: 100 μV; time interval 5 s.
Integration of NC lead;
NC, nucleus caudatus;
HV, formatio hippocampalis ventralis;
NMT, nucleus medialis dorsalis thalami;
FR, formatio reticularis mesencephali;
MC, cortex motoris

lacrimation, trembling, tachypnea, mydriasis, and decreased responsiveness to stimuli.

This complex of effects in the mescaline-treated rabbits was largely dependent, as regards intensity and duration, on the dose and on the time interval of the observation, being more pronounced (except for stupor) in the first hour after administration; in any case the animals had returned to their pre-injection condition 24 h later. With chronic administration of 100 μg/kg of mescaline the rabbits constantly exhibited the described stuporous condition: in some animals this symptom lasted until the next administration of the drug.

On the other hand, all the other symptoms faded away gradually beginning on the third day: mydriasis and salivation disappeared completely and there was a normalization of hind limb tone: tachypnea was only occasional. A considerable weight loss was manifested in all animals.

Effect of Mescaline on EEG Recording. Figure 4 reproduces typical phases of EEG obtained from the different recording sites in the rabbit, after a single intraventricular administration of mescaline (100 μg/kg, paradigmatically chosen). Figure 5 illustrates the pattern of electrogenesis of the area of nucleus caudatus but it is representative also of the other areas recorded in the brain of rabbits undergoing chronic treatment with 100 μg/kg mescaline.

Shortly after a single mescaline injection, the EEG resting pattern changes, in every recorded area, to one consisting of decreased voltage and fast waves. The duration of the arousal depends on the dose administered: after 10–40 min the voltage amplitude

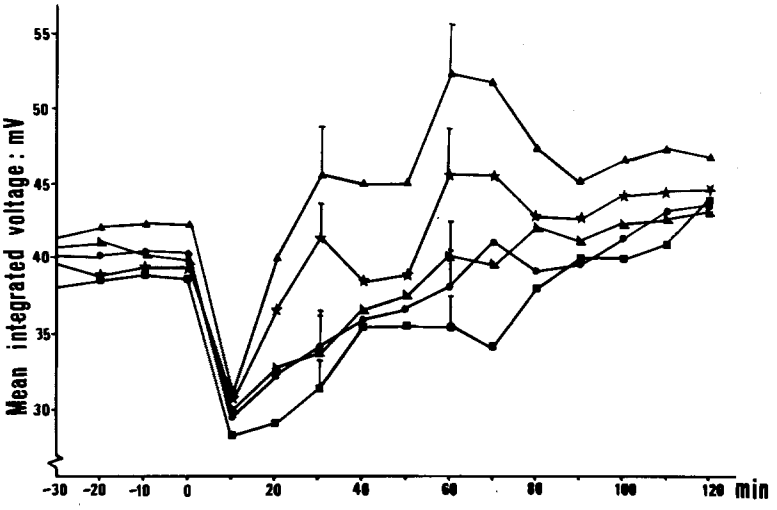

Fig. 5
Changes in rabbit electrogenesis after 100 µg/kg mescaline injected intraventricularly for 5 days. Integrated EEG is recorded from nucleus caudatus. Mean values of 8 animals with some standard errors.
▲——▲ 1st day; ★——★ 2nd;
◣——◣ 3rd day; ●——● 4th day;
■——■ 5th day.

returns to initial levels which are subsequently surpassed. Twenty-four hours after mescaline administration the recording had returned to its pre-injection pattern.

With repeated, daily, intraventricular injections of 100 µg/kg of mescaline, the time required for the recovery of the basic voltage becomes progressively more delayed from the third day onwards, the height of the tracing reaches its original levels only after the 80–90th min, and the phase of high voltage is no longer evident.

DISCUSSION

A clear-cut analgesic effect is shown, in the rabbit, for intraventricularly administered mescaline, by means of an electrical stimulation test of the dental pulp. A dose-effect relationship is also demonstrable with the development of a complete tolerance to antinociception after repeated administrations. A decreased response to pain was described for mescaline (Schwartz et al., 1956) as well as for other hallucinogenic drugs such as LSD and bufotenin (Evarts, 1956; Kanai et al., 1962) when injected intraventricularly. However, the phenomenon was not quantitated, nor was the development of tolerance demonstrated. The results of the present investigation also show the great variety of symptoms which follow mescaline application in the rabbit brain: the behavioral changes are in part similar to those observed by Schwartz et al. (1956) and by Sturtevant and Drill (1956) in the cat after intracerebral administration, with the difference that we have never observed epileptoid seizures. It must be noted, however, that higher doses of mescaline were used in the cat. A nearly complete tolerance is also demonstrable in the rabbit to most of the behavioral effects induced by mescaline by the end of 5 days of intraventricular administration, with the sole exception of the stuporous state which never disappeared. The tolerance to behavioral effects of mescaline shown in the rabbit is consistent with the tolerance to behavioral and rope-climbing performances shown in the rat by Freedman et al. (1958) after successive doses of mescaline, as well as of LSD. The confrontation of the data here presented with those of the literature on the subject seems therefore to indicate that common biochemical and neural patterns underlie some relevant pharmacologic effects of both mescaline and LSD. In the attempt to elucidate these patterns it seems useful to stress some similarities that emerge between the hallucinogen mescaline, object of the present investigation, and another class of drugs, the narcotic analgesics.

Analgesia elicited by morphine and the development of tolerance to this effect after intracerebroventricular administration, either in the rabbit (Hertz and Teschemacher, 1973), or in the rat (Ferri et al., 1974) exhibit kinetics very similar to those we have described for mescaline. Analogously, on the symptomatologic plane, the administration of the narcotic directly into the rat brain ventricle induces behavioral depression, stupor (Khazan, 1971) and, with an increase of doses, a catatonic-like posture alternating with periodical restlessness and running movements (Ferri et al., 1974). Moreover, work now in progress in our laboratory, which will be the object of a later communication, demonstrates the development of a cross-tolerance to antinociceptive as well as to be-

havioral effects between morphine and mescaline in the rabbit after intraventricular administration.

This complex of data seems to indicate, therefore, a convergence of morphine and mescaline, at least as regards certain pharmacologic effects in the same periventricular areas.

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