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Cross Tolerance to Antinociception Elicited by Intracerebroventricular Administration of Mescaline and Morphine to Rabbits, and EEG Correlates

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Abstract. Tolerance and cross tolerance to the antinociceptive effect of equipotent doses of morphine (10 μg/kg) and mescaline (100 μg/kg) are shown in the rabbit after their repeated intracerebroventricular administration. The recording of the electrical activity of different brain areas indicates that a partial tolerance also develops to the EEG effects in animals undergoing chronic treatment with mescaline.

The comparison of certain of the mescaline-induced effects with those of morphine suggests that some biochemical and neural patterns are common to the 2 drugs.

Key words: Mescaline – Morphine – Nociception – EEG.

In a previous paper we described that in the rabbit an acute treatment with mescaline elicits analgesia, the intensity of which is dose-dependent; with daily administration a complete tolerance develops to the antinociceptive effect (Ferri et al., 1975).

The purpose of the present study is to examine the possibility of a cross tolerance between mescaline and morphine antinociception in an attempt to provide evidence for a correlation between the 2 drugs which might indicate similarity in the mechanism of action.

Additional observations are also reported here concerning the electrical activity of the rabbit brain after treatment with mescaline, in order to determine the relationship between brain electrogenesis, and analgesia and tolerance development.

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MATERIAL AND METHODS

The experiments were performed on male adult rabbits weighing 2.5–3.0 kg.

Apparatus and Procedure. In order to study the cross tolerance between morphine and mescaline antinociception, the licking reaction test, based on electrical stimulation of the tooth pulp, was used (Cheymol et al., 1959). A hole about 1 mm in diameter extending almost to the pulp was drilled into a central point of the upper incisors and two gold stimulation electrodes were secured inside the holes with dental cement. 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 expressed in volts was verified every day for 5 days, from 10 min before the administration of the drugs until 120 min after.

In order to study the changes in the electrical activity of the brain following treatment with mescaline, stainless steel electrodes were implanted in the rabbit brains (under nembutal anesthesia) 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 brain potentials of the animals, placed in shielded cages, were recorded every day for 5 days on an 8-channel electroencephalograph (Mod. Neuro 20 Battaglia-Rangoni) for 40 min before the intraventricular administration of mescaline 100 μg/kg 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.

A stainless cannula was permanently implanted into the anterior horn of the right lateral ventricle for the ventricular application of the drugs (Feldberg and Sherwood, 1953).

Control animals received an equal volume of saline.

At the end of the experiments the cannula position was verified by means of an intraventricular dye injection and electrolytic lesions were also caused in order to confirm the position of the electrodes.

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

Substances and Schedule of Administration. Morphine sulphate (C. Erba), 10 μg/kg and mescaline sulphate (Merck) 100 μg/kg, both dissolved in saline solution, were administered intraventric-

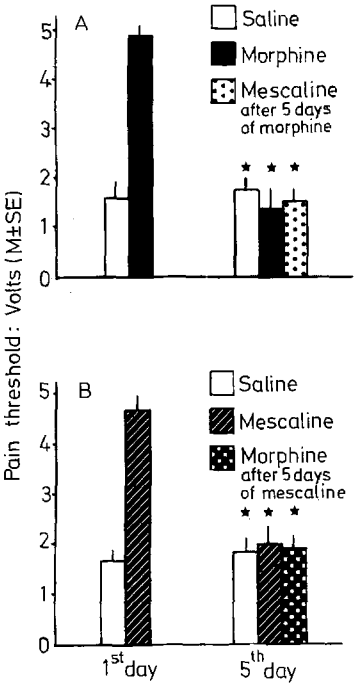

Fig. 1 A and B. Cross tolerance between equipotent analgesic doses of morphine (10 μg/kg) and mescaline (100 μg/kg) injected intracerebroventricularly into rabbit. Histograms indicate pain thresholds, expressed in volts. (Mean of peak effect ± S.E., of groups of 8 animals.) (A) At 5th day no significant difference ($P > 0.05$) among mean responses of animals treated with saline (open columns) or morphine (closed columns), or mescaline after morphine (dotted column). (B) At 5th day no significant difference ($P > 0.05$) among mean responses of animals treated with saline (open columns) or mescaline (hatched columns), or morphine after mescaline (checkered column)

ularly in a constant volume of 50 μl respectively to 2 different groups of 8 rabbits, once daily for 5 days. Single injections of the above doses of antinociceptive agents were approximately equipotent in the licking reaction test. On the fifth day, rabbits pretreated with mescaline were given 10 μg/kg morphine intraventricularly while the morphine-treated animals received 100 μg/kg mescaline.

RESULTS

Figure 1 (A and B) shows, first of all, that tolerance develops to the antinociceptive effect of mescaline as well as of morphine, during 5 days' treatment. A clear-cut cross tolerance is also detectable between morphine and mescaline: rabbits pretreated with mescaline when challenged with morphine exhibit a response to the nociceptive stimulus equal in intensity to that of animals treated for 5 days with morphine, and vice versa.

The pattern of electrogenesis in the area of the nucleus caudatus after acute or chronic administration of mescaline is illustrated in Figures 4 and 5 in the paper of Ferri et al., 1976. They also describe the patterns in the other areas recorded.

Shortly after the first mescaline injection the EEG resting pattern changes to one consisting of decreased voltage and fast waves; then the voltage amplitude returns to initial levels which are subsequently surpassed (Fig. 4 in Ferri et al., 1976). With repeated daily intraventricular injections of 100 μg/kg of mescaline, the time required for the recovery of the basic voltage progressively increases: the height of the tracing reaches its original levels only after 80–90 min and the phase of high voltage gradually disappears (Fig. 5 in Ferri et al., 1976).

DISCUSSION

The findings of the present investigation provide clear evidence for the possibility of a cross tolerance between a narcotic drug, morphine, and a hallucinogen, mescaline, as far as a specific pharmacologic activity is concerned. Besides antinociception and tolerance development to this effect, other similarities between morphine and mescaline emerge, even on a symptomatologic level: the administration of the narcotic directly into the brain ventricle induces, at least in the rat, behavioral depression, stupor (Khazan and Colasanti, 1971), and, with increased dosage, a catatonic-like posture alternating with periodic restlessness (Ferri et al., 1974)—thus a symptomatology similar to that already described for the hallucinogenic drug intraventricularly injected (Ferri et al., 1976). This complex of data would lead us to believe that there is a convergence of mescaline and morphine, as far as certain pharmacologic effects are concerned, in the same brain periventricular areas. However, the study of the changes in the electrical activity of the rabbit brain induced by mescaline and morphine respectively does not seem to give further support to this hypothesis. The electrical brain recording indicates discrepancy between the dual effect of mescaline (Fig. 5 in Ferri et al., 1976) and the dual effect of morphine on the EEG. In this respect, a single intraventricular dose of mescaline initially produces arousal patterns, as also described elsewhere (Takio and Himwich, 1965) and then a phase follows of progressively higher voltage. On the contrary, an intraventricular injection of morphine, in the rabbit as well as in the rat, initially produces EEG changes with high waves predominating, claimed to be characteristic of sleep, followed by persistent activation of the pattern (Navarro and Elliott, 1971; Khazan and Colasanti, 1971). For both drugs analgesia occurs shortly after administration, that is, in the first phase of EEG changes. There is good reason to doubt, however, that the EEG respon-

ses are correlated with nociception. Recent work by Oliverio (1975) points out this dissociation and correlates the EEG morphine responses more to the behavioral effects, at least in mice, than to the analgesia. On the other hand, the appearance of high voltage waves on the EEG following morphine would not actually represent a sleeplike activity of the CNS but rather a part of a dose-related continuum of an excitatory state (Nakamura and Winters, 1973). That morphine induces a continuum of CNS excitation is also suggested by Pinto Corrado and Longo (1965).

The disappearance of the EEG biphasic effect in the rabbit treated for 5 days with mescaline could be interpreted as a development of a tolerance, but only a partial one. This phenomenon recalls the desensitization of mescaline to the excitatory effect obtained in single cortical neurons after repeated or prolonged exposure to the drug (Bevan et al., 1974). In our experiments the normalization of the EEG tracing is not as complete as that described following chronic treatment with morphine, perhaps because the period of treatment was too short. In fact as far as the narcotic is concerned, a tolerance, shown by a return of EEG voltage to normal amplitude, develops in 8–15 days of treatment (Nakamura and Winters, 1973).

It would be useful, therefore, to prolong the period of administration in the case of mescaline as well, to arrive at a better understanding of the patterns underlying its pharmacologic effects.

Another approach to the problem might be the discovery of common biochemical patterns for morphine and mescaline. It is well known, in fact, that certain effects of morphine, including analgesia and tolerance development, may be correlated to the levels and turnover of neurotransmitters (Way and Shen, 1971). A similar relationship could therefore be postulated for mescaline as well.

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