TRANSCALLOSALLY EVOKED POTENTIALS AND THE EEG IN THE DECEREBRATE DOG: ACTIONS OF TRYPTAMINERGIC, DOPAMINERGIC AND ADRENERGIC AGONISTS *

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Curtis and Bard (1939) electrically stimulated the cortex in the monkey and evoked a biphasic wave in specific areas of the contralateral cortex. Curtis (1940a) described the transcallosally evoked potential (TEP) as a wave having a surface positive component followed by a longer lasting surface negative component. The TEP was abolished by sectioning the corpus callosum. Curtis (1940b) proposed that the surface positive component was due to afferent activity in the callosal fibers, whereas the negative component represented postsynaptic depolarization of interneurones. Although this interpretation has been challenged by Peacock (1957) and Grafstein (1959), the TEP has been used extensively by Marrazzi (1953, 1957) to study the activity of putative neurotransmitters and hallucinogens on cortical synaptic activity.

In previous studies in this laboratory, tryptamine, LSD-like hallucinogens and adrenergic agonists facilitated spinal reflexes in the chronic spinal dog (Martin and Eades, 1970) and in the acute decerebrate spinal cat (Vaupel and Martin 1971; Bell and Martin 1974). It has been proposed that the LSD-like hallucinogens act at tryptaminergic receptors to produce these facilitatory effects (Martin and Eades 1972). Kay et al. (1973) reported that tryptamine and LSD caused similar EEG changes in the encephale isolé cat. The observations by Martin et al. (1975a, 1976) that both the cerebral cortex and the corpus callosum contained tryptamine stimulated the present study on spontaneous and evoked cortical activity. The TEP seemed to be a relevant model for the study of the effects of tryptamine, LSD-like hallucinogens and adrenergic agonists on the EEG and cortical processes involving long interhemispheric axons.

Methods

Beagle-type dogs of either sex, weighing 6.0—13.5 kg, were used in the present study. The animals were anesthetized with ether and a tracheal cannula was inserted. Polygraphic recordings of arterial blood pressure were made from a pressure transducer connected to the catheterized femoral artery. All injections were made intravenously through the catheterized femoral vein. After the animal's head had been placed in a stereotaxic instrument, the calvarium was exposed and removed between stereotaxic coordinates AP 0.0 and A 30.0 (Lim et al. 1960). Ether anesthesia was discontinued, and the animal was decerebrated at the midpontine level by use of electrolytic coagulation. Following the transection the animal was placed on a respi-

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rator and end-tidal CO_2 was maintained at 3.5—4%. An 8 mg/kg injection of gallamine was given to facilitate control of respiration and to prevent movements. The cortex was exposed by cutting the dura. A dental acrylic well, filled with warm mineral oil, was fashioned on the calvarium surrounding the exposed cortex. The temperature of the mineral oil was automatically maintained at 37°C by use of a thermistor and an incandescent light. Body temperature was maintained at 37°C by means of a rectal thermistor probe and a heat lamp.

Silver-tipped recording and stimulating electrodes were spring-loaded to allow a constant light pressure on the cortical surface of the pulsating brain. The two stimulating electrodes were placed 1—3 mm apart on the g. ectolateralis of the right hemisphere, and the two recording electrodes were positioned on the homologous cortical site of the left hemisphere. The stimulus consisted of a square wave of 0.5 msec duration presented every 2 sec by a Grass S88 stimulator through a stimulus isolation unit. Recording signals of evoked potentials were sent through a high impedance probe and displayed on an oscilloscope. The amplified signal was recorded on electromagnetic tape for later computer analysis. The recording site was chosen by repositioning the recording electrode on the cortical surface until a satisfactory TEP was displayed on the oscilloscope. A satisfactory site was defined as one where the TEP could be increased to an amplitude of over 800 μV by increasing the strength of the stimulus and where the threshold of the TEP was less than 2 mA. After a suitable recording site had been found, the indifferent recording electrode was positioned to minimize the stimulus artifact. The stimilus voltage was adjusted to evoke a transcallosal potential whose negative component had an amplitude of approximately 400 μV.

A monopolar EEG recording was obtained from the cortex immediately adjacent to the site of the transcallosal recording. The signal from the EEG driver amplifier was connected to a Grass Model 10P integrator set at full wave rectification.

The TEP and the EEG were recorded immediately before the injection of all drug and control solutions and again at various times thereafter. Recording periods were 2 min long from which 50 evoked potentials were later computer averaged using a Culver Sigsys program. The effects of experimental drugs were determined by changes in the amplitude of the positive and negative components of the TEP and were compared to the amplitude after saline infusion using related and independent *t*-tests. The EEG was analyzed by visual inspection and by amplitude integration. The latter method involved determining the "electrogenesis", the average integrator output in 20 sec, during the 2 min recording periods.

The delta index from EEG recordings was determined by counting the number of waves with frequencies less than 4 c/sec during 20 sec intervals of the control period and at the peak of the drug effect. The means were compared by the use of a related *t*-test.

Freshly prepared solutions of the following compounds in physiological saline were used in this study: apomorphine HCl; tryptamine HCl and dimethyltryptamine (DMT); methoxamine ("Vasoxyl"); lysergic acid diethylamide (LSD) and mescaline HCl. Solutions of pentobarbital ("Nembutal"), and gallamine ("Flaxedil"), were commercially prepared. Tryptamine (10 and 20 mg/kg), apomorphine (5 mg/kg) and methoxamine (0.88 mg/kg) were infused over 10 min. LSD (30 μg/kg), DMT (1 mg/kg), mescaline (6 mg/kg) and pentobarbital (30 mg/kg) were infused over 20 min. Each compound was given to at least four animals.

The doses of tryptamine, LSD, mescaline, methoxamine and DMT were selected because they caused an equivalent facilitation of the flexor reflex in the chronic spinal dog (Martin and Eades 1970; D.B. Vaupel, personal communication). Apomorphine, a potent dopamine agonist (Ernst 1967) depresses the flexor reflex in the chronic spinal dog and

causes a mydriasis comparable to the above-mentioned drugs (Martin et al. 1975b). An anesthetic dose of pentobarbital was studied because Marrazzi (1953, 1957) used pentobarbital-anesthetized animals to study the effects of various drugs on the TEP.

Results

The TEP has a biphasic waveform consisting of an initial positive deflection followed by a longer lasting negative deflection. The latency of the positive and negative waves was determined by examining the computer printouts. The latency was the time from the onset of the stimulus artifact to the point of positive or negative inflection. The average latency of the positive wave was 2.1 msec (SEM = ±0.11), and the average latency of the negative wave was 8.1 msec (SEM = ±0.31).

Fig. 1 shows the changes in the TEP following 20 min infusions of LSD, mescaline and DMT. The latency of the positive or negative component of the TEP was unaffected by the hallucinogens. DMT caused a significant (126 ± 7.0% of control) increase in the amplitude of the positive wave. The negative wave was decreased by LSD, increased by DMT and remained unchanged following the infusion of mescaline. The effects of these drugs on the negative component of the TEP are further illustrated in Fig. 2, which shows the time-action curves for the hallucinogens. LSD caused a significant and persistent decrease in the amplitude of the negative wave, whereas the DMT-induced increase was transient. Mescaline caused a gradual increase in the ampli-

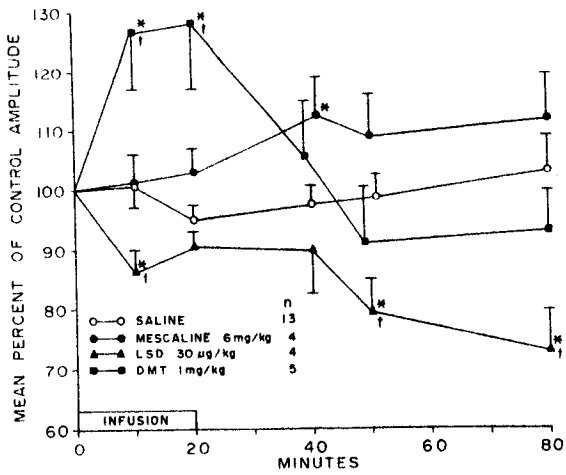

Fig. 2. Each point represents the percent of control amplitude (mean ± SEM) of the negative component of the TEP. (*) Significantly different from saline ($P < 0.05$; t test, independent samples). (+) Significantly different from saline ($P < 0.05$; t test, related samples).

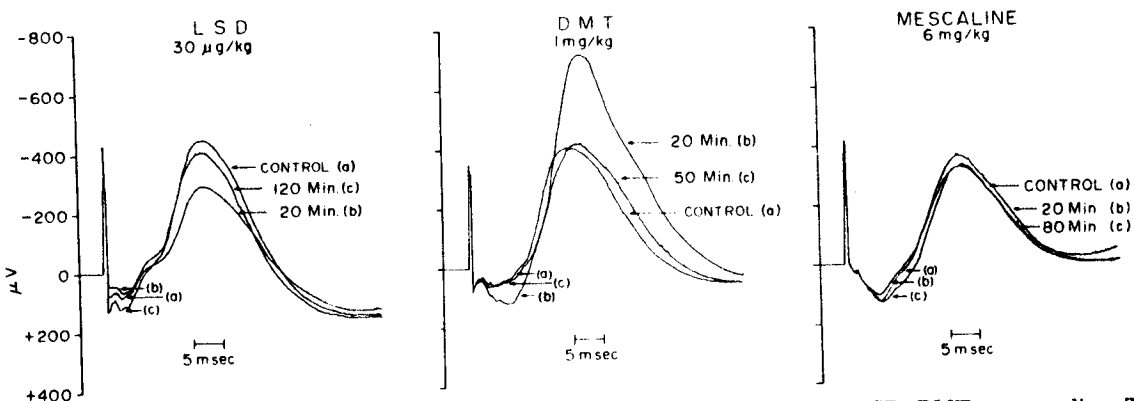

Fig. 1. Computer printouts of the TEP from each of three animals given either LSD, DMT or mescaline. The inital negative deflection is the stimulus artifact. The lines in each printout represent the average of 50 potentials before (a), at the end of (b) and after (c) the infusion of the drug. The positive and negative components of the TEP are indistinguishable at the times shown for the mescaline infusion.

TABLE I

THE EFFECT OF TRYPTAMINE, APOMORPHINE AND METHOXAMINE ON THE NEGATIVE COMPONENT OF THE TEP

Figures represent the per cent of control amplitude (mean ± SEM) during the last 2 min of drug infusion and 20 min later.

Drug	Number of observations	8—10th minute	20 min after infusion
Saline	14	101 ± 4.4	92 ± 4.6
Tryptamine 1 mg/kg/min	5	106 ± 10.0	103 ± 6.1
Tryptamine 2 mg/kg/min	5	92 ± 7.2	112 ± 7.0
Apomorphine 0.5 mg/kg/min	5	103 ± 6.9	96 ± 3.2
Methoxamine 0.088 mg/kg/min	4	116 ± 6.2	97 ± 4.2

tude of the negative wave which was significantly different from saline only at 40 min. Tryptamine, apomorphine and methoxamine were infused over 10 min. These agents did not significantly change either the latency or the amplitude of the positive and negative waves of the TEP. The effects of tryptamine, apomorphine and methoxamine on the amplitude of the negative wave are presented in Table I.

The cortical EEG of the midpontine, pretrigeminal animal was one of synchrony with occasional episodes of low voltage patterns with frequencies in the alpha range (10—12 c/sec). During the infusion of DMT, there was a marked increase in the amplitude and the density of the slow waves. The delta index increased from 22.1 ± 2.6 to 36.3 ± 1.2 ($P < 0.003$). LSD caused a slight but non-significant increase in the delta density and, like DMT, increased the amplitude of the slow waves. Mescaline, on the other hand, caused a slight decrease in the slow wave components of the EEG. These results are further illustrated by amplitude integration as presented in Fig. 3. The electrogenesis increased during the infusion of DMT to levels that differed significantly from saline controls. LSD caused a non-significant, but persistent, increase in electrogenesis, whereas mescaline decreased it. Tryptamine, apomorphine and methoxamine had no significant effects on electrogenesis as shown in Table II.

At the conclusion of 5 experiments an anesthetic dose (30 mg/kg) of pentobarbital was infused over 20 min. Pentobarbital significantly increased the amplitude of the positive component of the TEP (130 ± 4.9 % of control) and significantly decreased the amplitude of the negative wave (58 ± 9.6% of control). These effects were evident at the end of the infusion and for at least 20 min thereafter. Pentobarbital caused a concomitant increase in electrogenesis that was significantly above predrug levels (156 ± 7.6% of control).

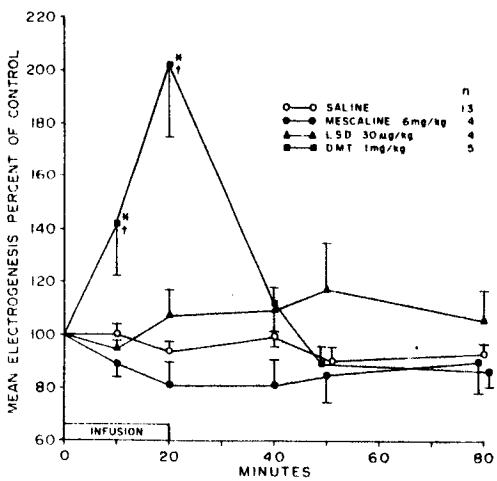

Fig. 3. Each point represents the percent of control electrogenesis (mean ± SEM). (*) Significantly different from saline ($P < 0.05$; t test, independent samples). (+) Significantly different from saline ($P < 0.05$; t test, related samples).

TABLE II

THE EFFECT OF TRYPTAMINE, APOMORPHINE AND METHOXAMINE ON ELECTROGENESIS

Figures represent the per cent of control electrogenesis (mean ± SEM) during the last 2 min of drug infusion and 20 min later.

Drug	Number of observations	8—10th minute	20 min after infusion
Saline	14	101 ± 2.7	102 ± 3.8
Tryptamine 1 mg/kg/min	5	86 ± 7.5	93 ± 9.5
Tryptamine 2 mg/kg/min	5	102 ± 11.9	110 ± 9.9
Apomorphine 0.5 mg/kg/min	5	102 ± 4.6	101 ± 4.0
Methoxamine 0.088 mg/kg/min	4	113 ± 9.6	118 ± 7.0

Discussion

Tryptamine has been isolated in the spinal cord of the dog where it is thought to be localized in long ascending and descending fibers (Martin et al. 1975a). Tryptamine and the LSD-like hallucinogens have similar spectra of pharmacologic action in the chronic spinal dog (Martin and Eades 1970). These effects included facilitation of the flexor reflex and evocation of the stepping reflex, mydriasis and tachycardia. The actions of both tryptamine and the LSD-like hallucinogens could be selectively blocked by cyproheptadine in dose levels which have little action of their own. Furthermore, LSD tolerant dogs were cross tolerant to the effects of tryptamine (Martin and Eades 1972). The doses of LSD, DMT and mescaline used in the present study and in those with chronic spinal dogs are known to be hallucinogenic in man (Wolbach et al. 1962; Rosenberg et al. 1964). Tryptamine infusions in humans caused LSD-like physiological actions and perceptual distortions (Martin and Sloan 1970). These studies suggest that the LSD-like hallucinogens act as agonists at tryptaminergic receptors.

Tryptamine has also been found in the cerebral cortex and the corpus callosum of the dog (Martin et al. 1976). We anticipated that the tryptaminergic agonists would have qualitatively similar effects on the TEP. However, the results of the present study did not support this expectation.

Tryptamine had no effect on the amplitude of the TEP, whereas LSD decreased it and DMT increased it. The LSD-induced reduction of the TEP confirms the reports of Marrazzi (1957) and Purpura (1957). Marrazzi (1957) also reported that mescaline, norepinephrine and epinephrine decreased the TEP. Results obtained in these experiments are not easily reconciled with the latter findings of Marrazzi (1957). Neither mescaline nor methoxamine, a centrally acting α-adrenergic agonist (Martin and Eades 1970; Vaupel and Martin 1976), in dose levels that produced facilitation of spinal cord reflex activity comparable to that of LSD, altered the TEP. Since Marrazzi (1957) administered drugs close arterially in a bolus it is difficult to compare dose levels. A steady state was achieved in the present study through the use of long-acting agonists or the infusion of agonists. Yet another difference between experiments is that ours were done on unanesthetized decerebrate dogs, whereas those of Marrazzi (1957) were performed in pentobarbital-anesthetized cats. In the present study pentobarbital increased the amplitude of the positive component of the TEP and reduced the amplitude of the negative wave. How pentobarbital would influence the actions of other drugs on the TEP is not known. Indeed, Wikler (1954) reported that pentobarbital sup-

pressed mescaline hallucinations in man. The neuropharmacologic action of pentobarbital may have confounded the effects of the experimental drugs used by Marrazzi (1953, 1957). Regardless, it is clear that if there are transcallosal tryptaminergic fibers, their physiologic role has not been clarified by this study.

Globus and Scheibel (1967) have found that callosal fibers and fibers from unidentified sources terminate on oblique dendritic processes of pyramidal cells. Purpura (1957), Grafstein (1959) and others have suggested that the negative component of the TEP was due to depolarization of dendrites near the cortical surface. The pyramidal dendrites described by Globus and Scheibel (1967) may be among those involved. The neurotransmitter responsible for their depolarization is not known. The results of this study suggest that tryptaminergic, dopaminergic and adrenergic processes are probably not involved. Marrazzi (1953) has suggested a cholinergic mechanism.

The effects of microiontophoretic application of LSD-like hallucinogens to cortical cells are difficult to reconcile with the present results as well as those of Marrazzi (1957). Boakes et al. (1970) reported that LSD inhibited cellular firing in the decerebrate cat. Krnjević and Phillis (1963) reported that LSD, mescaline, DMT, tryptamine, dopamine and epinephrine depressed firing of cortical cells in anesthetized and unanesthetized cats. Bradshaw et al. (1971) and Bevan et al. (1974) reported that mescaline had excitatory and inhibitory effects on cortical cell firing in halothane-anesthetized cats. However, cellular firing rates may not be a critical factor in the generation of the TEP.

The effects of LSD-like hallucinogens on the TEP could be influenced or mediated indirectly through their effects on the cortical EEG and reticular activating system. Grafstein (1959) reported that the amplitude of the positive wave was greater in the absence of spontaneous cortical electrical activity. A comparable state may have been produced in this study by pentobarbital and DMT. Both of these compounds significantly increased the amplitude of the positive wave, however DMT increased and pentobarbital decreased the amplitude of the negative wave of the TEP. DMT and to some extent LSD caused EEG hypersynchrony, whereas mescaline had little effect. Hallucinogen-induced EEG synchrony has been reported by others. Bradley and Marley (1965) and Takeo and Himwich (1967) reported that DMT caused EEG hypersynchrony. LSD caused high voltage slow wave activity in the cat (Adey et al. 1962; Winters and Wallach 1970). Fairchild et al. (1967) and Winters and Wallach (1970) reported that mescaline caused hypersynchrony at doses above those in the present study. Pickworth and White (1977) reported tryptamine-induced EEG synchrony in rabbits. It should be noted that while integrated amplitude provides a quantitative index of EEG changes, it does not differentiate qualitatively distinct EEG states of a similar amplitude.

Other studies, as discussed above, indicate that LSD, DMT, mescaline and tryptamine have qualitatively similar effects on the flexor reflex, the firing rates of cortical neurons, and the EEG. There is also evidence that these drugs are hallucinogenic in man. Nevertheless, the results of the present study show that they have dissimilar effects on the TEP and thus are not correlated with hallucinogenic activity. It is, therefore, concluded that synapses and neurons mediating the TEP are not involved in the LSD-type hallucination.

Summary

The midpontine decerebrate dog, immobilized with gallamine, was used to determine the changes in the transcallosally evoked potential (TEP) produced by intravenous infusions of various drugs. A total of 50 TEPs, recorded from the g. ectolateralis, was computer analyzed before, during and after administration of the drugs. Changes in the TEP were also correlated with changes in the

EEG recorded from the g. ectolateralis. The EEG was analyzed by inspection and amplitude integration (electrogenesis). LSD (30 μg/kg) significantly depressed the TEP, and the effect persisted for at least 80 min. DMT (1 mg/kg) caused a significant and reversible increase in the amplitude of the TEP. LSD and DMT reduced the alpha activity of the EEG and enhanced the amplitude of the low-frequency waves. DMT produced a significant and LSD a marginal increase in electrogenesis. Tryptamine (10 and 20 mg/kg), mescaline (6 mg/kg), methoxamine (0.88 mg/kg) and apomorphine (5 mg/kg) had no significant effect on the TEP or EEG. These results suggest that depression of the TEP is not related to spinal reflex facilitation in the dog or hallucinogenic activity in man.

Résume

Potentials évoqués par voie transcallosale et EEG chez le chien décérébré: action des agonistes tryptaminergiques, dopaminergiques et adrénergiques

Le chien décérébré midpontin, immobilisé par gallamine, est utilisé pour préciser les modifications du potential évoqué par voie transcallosale (TEP) produites par installation intraveineuse de diverse drogues. Un total de 50 TEPs, enregistrés au niveau du gyrus ectolatéralis, a été par ordinateur avant, pendant, et après administration des drogues. Les modifications du TEP sont également corrélées avec les modifications de l'EEG enregistré au niveau du gyrus ectolatéralis. L'EEG est analysé par inspection et par intégration d'amplitude (électrogenèse). Le LSD (30 μg/kg) déprime de façon significative les TEPs, et cet effect persiste au moins 80 minutes. Le DMT (1 mg/kg) provoque une augmentation significative d'amplitude du TEP, le LSD et le DMT diminuent l'activité alpha de l'EEG et augmentent l'amplitude des ondes de basse fréquence. Le DMT provoque une augmentation significative et le LSD une augmentation minime de l'électrogenèse. Le tryptamine (10 et 20 mg/kg), la mescaline (6 mg/kg) la méthoxamine (0.88 mg/kg) et l'apomorphine (5 mg/kg) n'ont pas d'effet significatif sur le TEP ni l'EEG. Ces résultats suggèrent que la dépression du TEP n'est pas liée à la facilitation spinale réflexe chez le chien, ni à l'activité chez l'homme.

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