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THE CEREBRAL ELECTROGRAPHIC CHANGES INDUCED BY LSD AND MESCALINE ARE CORRECTED BY FRENQUEL[1,2]

FRANCO RINALDI[3] AND H. E. HIMWICH

LSD (d-lysergic acid diethylamide), an alkaloid derived from ergot, produces in human subjects mental disturbances consisting of visual hallucinations and other psychotic symptoms. This phenomenon has been widely investigated because the LSD-evoked symptoms are similar to those of schizophrenic patients (1, 8, 12, 20, 23, 31, 34, 42, 44, 46, 47). Mescaline is another alkaloid long known to produce hallucinations and other psychological and somatic changes like those caused by LSD (2, 23, 31, 34). LSD affects the electrical activity of the brain of experimental animals and of human beings, diminishing or eliminating the slower rhythms, increasing the average frequency, introducing fast low voltage activity as well as causing a general diminution of voltage (3, 5, 13, 14, 22).

Frenquel (alpha-4-piperidyl benzhydrol hydrochloride) is a new non-hypnotic drug that renders animals less active (4) and is being applied in clinical psychiatry with promising results in the treatment of some psychiatric conditions (17, 41). Recently Fabing (17) reported that the psychotic symptomatology produced with LSD in human subjects could be corrected by the administration of Frenquel.

In our experiments on rabbits we studied the cerebral electrical activity of different brain structures as modified by LSD and mescaline, as well as by the subsequent administration of Frenquel.

METHODS

All our experiments were performed in unanesthetized, curarized rabbits maintained by artificial respiration. For recording the electrical activity of the brain, openings of a proper size to hold firmly coaxial electrodes were made in the skull. The surface of the stainless steel outer electrodes was in contact with the dura. The inner electrodes, made of stainless steel needles covered with insulating varnish except at the tip, penetrated the brain for recording from subcortical structures. Eight such electrodes were placed; the surface electrodes recorded from the motor and limbic areas of both sides of the cortex, and the deep electrodes from the head of the caudate nuclei and the medial thalamus. Another bipolar coaxial stimulating electrode of stainless steel with a distance of 2 mm. between the two bare tips was placed in the medial reticular substance of the midbrain at the level of the anterior quadrigeminal body. Methods and coordinates for the placement of such electrodes were previously described (38). The intracerebral electrode tract and the site corresponding to the tip of each subcortical electrode were checked by means of serial sections of the whole brain according to the staining technique previously described (38).

Cerebral electrical activity was recorded by means of an 8 channel electroencephalographic instrument, Grass D-3; one channel being used for recording the ECG. A Grass stimulator model S-4 was employed for electrical stimulation of the midbrain reticular formation. Parameters for stimulation of that formation and its effects on cerebral electrical activity were described in detail in a previous publication (38).

The drugs employed in this study were as follows: d-lysergic acid diethylamide (LSD-25) 0.1% solution, Sandoz Chemical Works, Inc.; alpha-4-piperidyl benzhydrol hydrochloride (Frenquel), The Wm. S. Merrell Co.; atropine sulfate 1.0% solution; chondodendron tormentosum extract, purified (Intocostrin), E. R. Squibb and Sons; mescaline sulfate, S. B. Pennick and Co.; isofluorophate (DFP); d-, l-amphetamine sulfate, Smith, Kline and French; alpha-2-piperidyl benzhy-

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[3] Fulbright Fellow, on leave from the Clinic for the Diseases of the Nervous System of the University of Cagliari, Cagliari, Italy.

drol hydrochloride (Meratran), The Wm. S. Merrell Co.; pentobarbital sodium (Nembutal), Abbott Laboratories; Chlopromazine hydrochloride (Thorazine), Smith, Kline and French.

All drugs were administered intravenously.

Results

The control electrical activity of the brain of rabbits in our experimental conditions exhibited an alternation of two main patterns which are illustrated by the records in figure 1. The left section of the record shows the resting or sleeping pattern which is present as long as the animal is left undisturbed and resting quietly. It consists of slow (1–3 cps.) high voltage waves and spindles of 14 cps. waves more prominent in the motor cortex. In the thalamus a 2–3 cps. activity appears mixed with 6 cps. waves. An accidental or purposely-induced sensory stimulus such as sound, touch or pain, or an electrical stimulation of the brainstem reticular formation breaks up the resting pattern, replacing it by the alert one. In the record of figure 1 the alerting response (right section of the record) was elicited by direct electrical stimulation of the midbrain reticular formation (unidirectional square pulses of a frequency of 300 cps., 2 milliseconds duration, an intensity of 1.5 v. for a period of 1.5 seconds). The alert pattern consists of a 7–4 cps. rhythm of maximal amplitude in the leads from the medial thalamus, but is also apparent in the cortical leads. Caudate and cortical activities are characterized also by low voltage fast activity (20–30 cps.).

LSD was administered in progressively increasing amounts from 1 to 60 gamma/kg. With amounts of the drug between 1 and 5 gamma/kg. an increasing facilitation of the pattern of alerting responses was observed. Minimal accidental noises were sufficient to induce an alert record, and the threshold of electrical stimulation of the reticular formation was slightly lowered. Larger doses between 10 and 15 gamma/kg. enforced this effect so that finally all features of sleep (slow waves and spindles) were abolished and the record exhibited only the characteristics of an enduring electrographic alertness (fig. 2). This pattern persisted for a period of 1½ hours. By the use of still larger doses of LSD we observed a phenomenon which so far has remained unnoticed. Large amounts (20–60 gamma/kg.) reversed entirely the electrographic picture so that the slow waves and sleep spindles reappeared and persisted. With these larger doses it was also observed that the production of the electrographic arousal required stronger sensory stimulation and that the electrical threshold of the reticular formation was perceptibly increased. However, no complete block of the alerting response was ever observed even with the administration of 100 gamma/kg., a dose given to 3 animals only.

The administration of mescaline produced

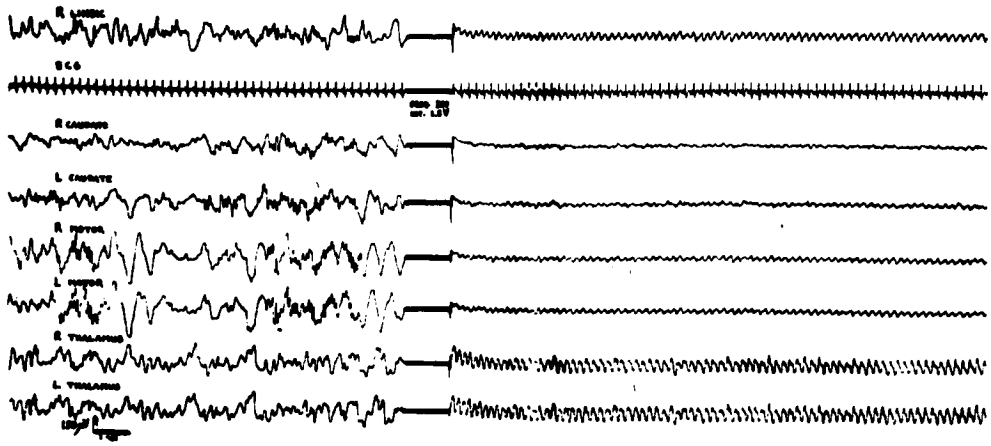

Fig. 1. Cerebral electrical activity of the curarized unanesthetized rabbit. The leads are (from the top tracing to the bottom one): (1) right limbic cortex, (2) ECG, (3) right caudate nucleus, (4) left caudate nucleus, (5) right motor cortex, (6) left motor cortex, (7) right thalamus, (8) left thalamus. (See description in text.)

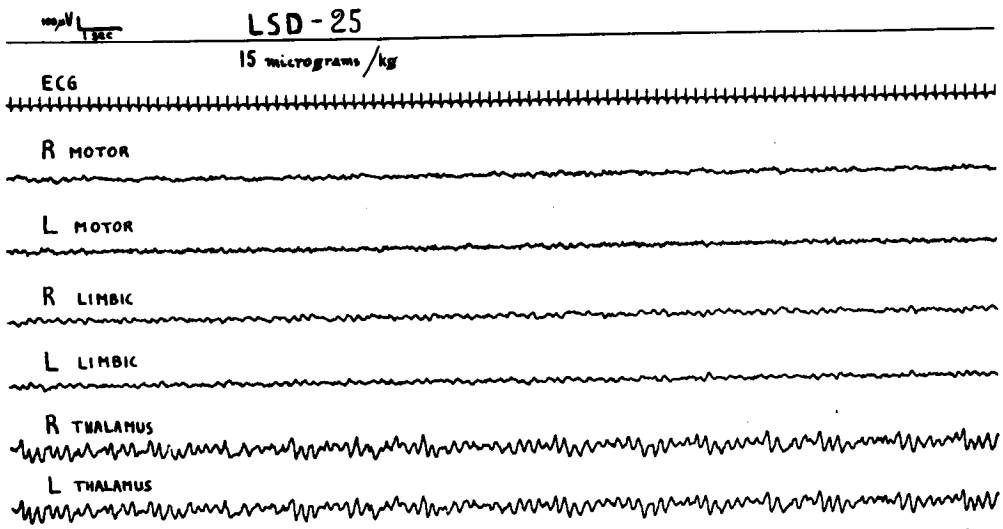

FIG. 2. Effect of LSD (15 gamma/kg.) on the cerebral electrical activity of the rabbit. Notice the low voltage fast activity in the motor cortex, the thalamic 4–6 cps. rhythm and the absence of high voltage slow waves and of spindles. The leads are (from the top tracing to the bottom one): (1) ECG, (2) right motor cortex, (3) left motor cortex, (4) right limbic cortex, (5) left limbic cortex, (6) right thalamus, (7) left thalamus.

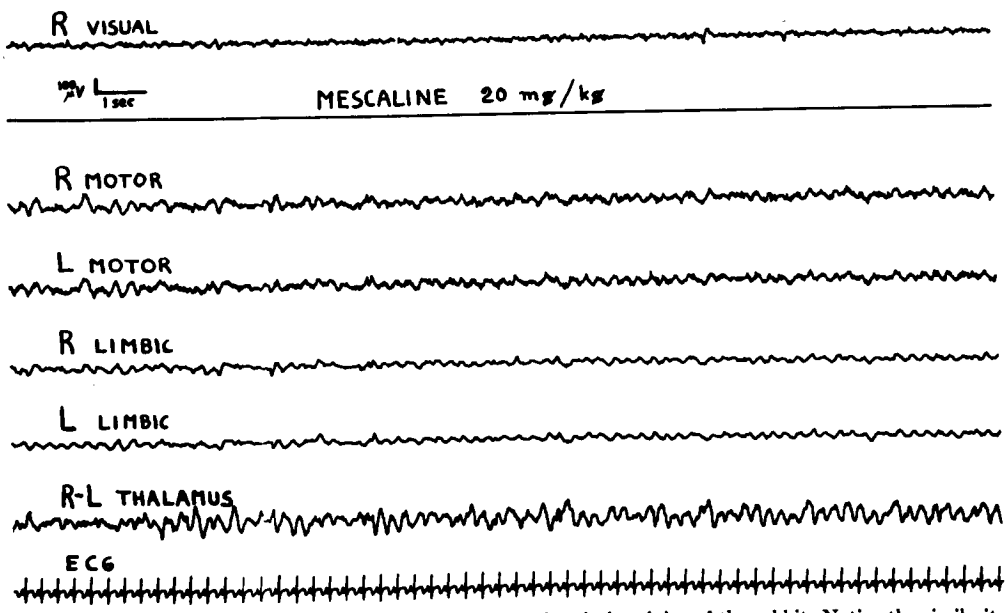

FIG. 3. Effect of mescaline (20 mg./kg.) on the cerebral electrical activity of the rabbit. Notice the similarity of this picture with that induced by LSD (fig. 2). The leads are (from the top tracing to the bottom one): (1) right visual cortex, (2) right motor cortex, (3) left motor cortex, (4) right limbic cortex, (5) left limbic cortex, (6) right-left thalamine (bipolar), (7) ECG.

changes similar to those of small doses of LSD. Mescaline given intravenously in amounts between 5–10 mg./kg. evoked an electrographic picture of alertness with the disappearance of the slow waves and spindles of sleep (fig. 3). Differently from LSD, no reversal of the alert pattern was observed with still larger doses of mescaline.

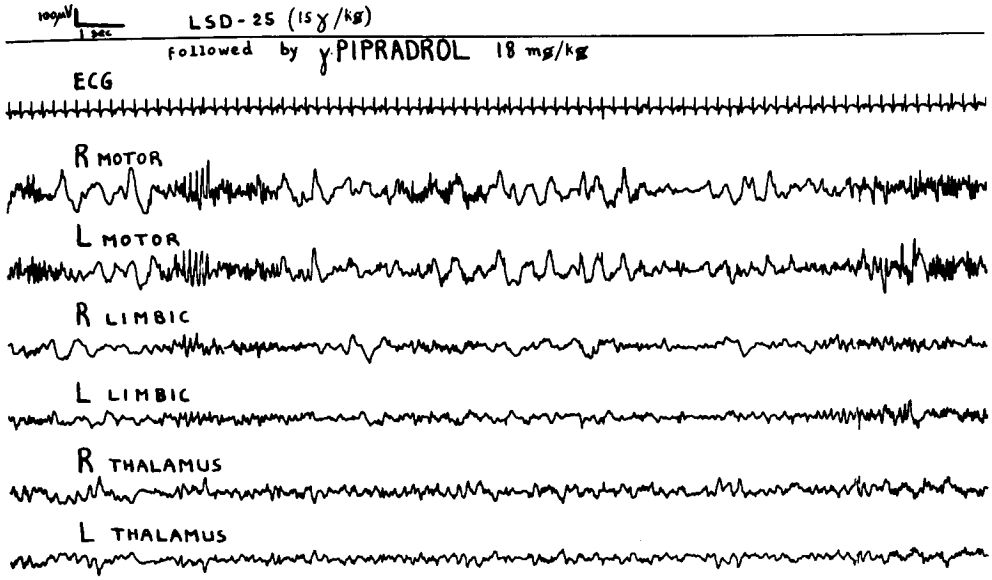

FIG. 4. Correction of the changes induced by LSD in the cerebral electrical activity of the rabbit by the administration of Frenquel (indicated in the figure as gamma-pipradrol). Notice the restoration of the spindles and slow waves typical of the resting pattern. Leads as in figure 2.

As soon as the alerting effect of the hallucinogenic drugs was fully developed, Frenquel was administered i.v. in progressively increasing doses from 1 to 30 mg./kg. It was observed that in amounts of 15–20 mg./kg. Frenquel corrected the electrographic changes induced by LSD (10–15 gamma/kg.), restoring the spindles and slow waves (fig. 4). With somewhat larger amounts (15–25 mg./kg.) Frenquel also eliminated the alerting effect of mescaline thus causing the sleep pattern to reappear (fig. 5).

The action of hallucinogenic drugs in producing an electrographic pattern of alertness is not a specific one. In fact a number of drugs give rise to a similar phenomenon. First will be listed cholinergic drugs, such as DFP, which stimulate specifically the mesodiencephalic activating system, the structure responsible for the production of the electrical alerting responses (38, 39). Other drugs that arouse electrical alertness are CNS stimulants like amphetamine and Meratran (40). Because of this lack of specificity for the changes induced by LSD and by mescaline, it seemed necessary to determine whether the corrective action of Frenquel was also non-specific. We therefore administered Frenquel in the same amounts and with the same technique, as in the experiments with the hallucinogenic drugs, to animals which had received doses of DFP (0.2 mg./kg.), of amphetamine (10 mg./kg.), or of Meratran (6 mg./kg.), sufficient to produce a permanent pattern of alertness similar to that caused by the hallucinogens. But Frenquel in any dosage failed to correct or to modify the electrical picture induced either by DFP, amphetamine or Meratran.

Previous work (40) showed that Frenquel alone, in the dosage with which it corrected the effects of hallucinogenic drugs, did not modify the spontaneous brain electrical activity of unpremedicated animals, for it did not enforce slow waves and spindles typical of the resting pattern, nor prevent the alerting response to physiological stimuli. Other drugs, unlike Frenquel, have the property of depressing the alerting mechanism and introducing the resting electrographic picture. First may be listed atropine (38, 39) which specifically paralyzes the mesodiencephalic activating system. Chlorpromazine is another drug which in small doses acts on the brain electrical activity as does atropine (40). Barbiturates, such as pentobarbital, also impose

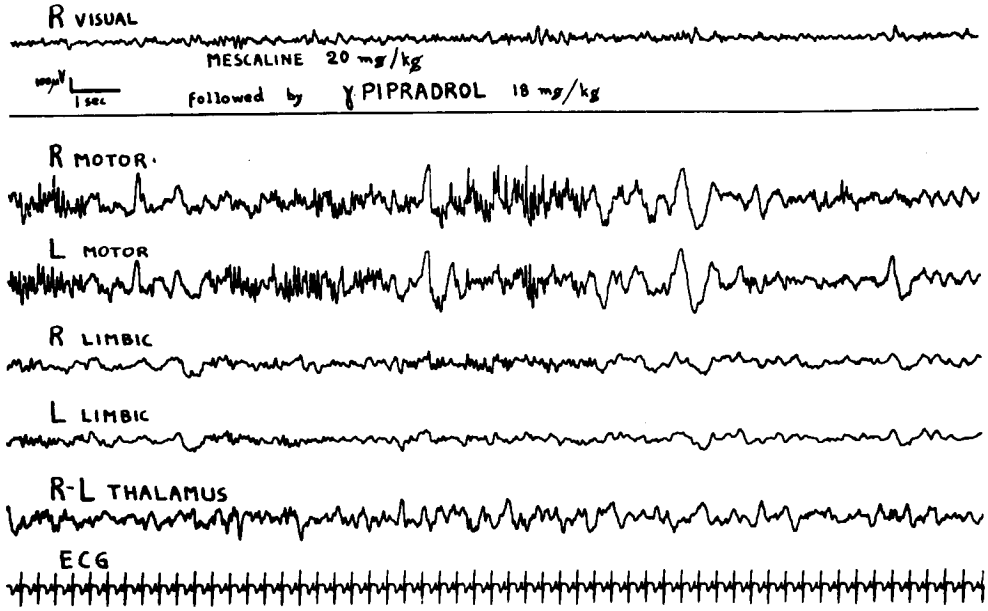

FIG. 5. Correction of the changes induced by mescaline in the cerebral electrical activity of the rabbit by the administration of Frenquel (indicated in the figure as gamma-pipradrol). Notice the restoration of the spindles and slow waves typical of the resting pattern. Leads as in figure 3.

the electrographic sleeping pattern (37). These three drugs in appropriate amounts eliminate the picture of alertness produced either by DFP, amphetamine or Meratran. Similarly either atropine (3 mg./kg.), Chlorpromazine (3 mg./kg.) or pentobarbital (15 mg./kg. i.p.), administered after the hallucinogenic drugs, corrected the pattern of alertness produced by LSD or mescaline, restored the features of sleep and depressed the arousal response to physiological stimuli.

Because LSD evoked a reversal in action when passing from small to large doses, we tested the influence of Frenquel after large doses of LSD. But after such doses of LSD as 20–60 gamma/kg. Frenquel did not change the cerebral electrographic pattern which remained a resting one.

DISCUSSION

The alert electrographic pattern caused by the hallucinogenic drugs in our experiments is concordant with the observations of other authors in animals and in man. Delay and coworkers (13) observed in the rabbit that LSD produced a flattening of the electrographic record due to the disappearance of the higher voltage components. A similar phenomenon was observed in cats by Elkes and associates (14) who furthermore reported that in cats LSD completely abolished the sleeping electroencephalographic features of moderate barbiturate anesthesia (without changing the behavioral anesthesia). Our experiments with LSD showed clearly that the flattening of the electrographic record was not due to a disappearance of cortical electrical activity but rather to the long lasting presence of a pattern of alertness, practically indistinguishable from the normal one (fig. 2). Since the waves of the alert pattern are all of very low amplitude, at least in the corticogram, it is obvious that the immediate impression is that LSD flattens the cortical record.

It is known that the disappearance of the slow rhythms of sleep and the introduction of the alert pattern are due to the activity of a brainstem mechanism with diffuse projection over the entire cortex, the mesodiencephalic activating system (MDAS), which includes the brainstem reticular formation of Moruzzi and Magoun (32) and the thalamic diffuse projection system of Jasper (24). The MDAS

is excited physiologically by impulses coming from collaterals of the sensory lemnisci and branching into the brainstem tegmentum. The excitation of the MDAS can also be produced experimentally by direct electrical stimulation of the cephalad portion of the brainstem reticular formation as in our experiments. Following the stimulation of the MDAS a diffuse desynchronization of the activity of the cerebral cortex occurs, wiping off the slow rhythms of sleep and introducing cortical fast low voltage and a 4–7 cps. thalamic rhythm (fig. 1). The desynchronization of the corticogram is supposed to subserve the state of alertness and also to afford a background of cortical activity or cortical tonus which probably is of importance in the regulation of the level of consciousness, awareness and mental activity. Many drugs can produce electrographic patterns of alertness, and some of them stimulate the MDAS directly. Such a direct effect has been established for the cholinergic drugs like DFP (38, 39). In the case of the alertness evoked by such hallucinogenic drugs as LSD it is not known whether a direct effect on the MDAS is involved. In fact observations of Elkes *et al.* (14) cast a well-founded doubt upon this hypothesis. They observed that LSD is unable to desynchronize the cortical activity in the "encephale isole" sleep pattern. This suggests that the alert picture produced by LSD in the normal animal is not due to a direct action as the MDAS but rather to an increased inflow of alerting stimuli to that formation by a mechanism not yet determined. In any case it remains a fact that in the normal animal the activating mechanism appears overactive with LSD in amounts from 5 to 15 gamma/kg., dosages comparable to those producing a psychotic-like state in man. The observations on the action of LSD on the EEG of humans are also concordant with the findings in animals. Rinkel and coworkers (42) observed mild electrographic changes due to the administration of LSD in normal and psychotic patients consisting in an increase of a few cps. of the alpha frequency, together with diminished responsiveness to hyperpnea, which means interference with the production of slow high voltage waves characteristic of hyperpnea. Gastaut and coworkers (22) studied human volunteers and noted that LSD accelerated the alpha rhythm, while decreasing its amplitude and regularity. In addition low voltage fast rhythms similar to the beta frequency appeared in the central regions of the skull and at times became generalized. Bradley and coworkers (3) studied the responsiveness of the alpha rhythm to eyes opening and to light stimuli. These authors found that normal human volunteers who before the administration of LSD exhibited poor or no responsiveness to eyes opening and to attention, that is to say poor desynchronization, presented a ready desynchronization after LSD, together with a decrease in the amplitude of the alpha waves.

It is interesting to note the analogy between the EEG alterations induced by the hallucinogenic substances and the records often obtained from schizophrenic and other psychotic patients (6, 9, 10, 11, 15, 18, 19, 26, 27, 28, 29, 33, 35, 43). We refer to the "choppy" rhythm and similar low voltage fast records accompanied by poor alpha organization first described by Pauline Davis (9, 10, 11). With Sulzbach she reported (11) the effect of mescaline on the EEG of normal subjects and was struck by the similarity between the choppy rhythm produced by mescaline and the one observed in a number of schizophrenic patients. This rhythm occurred simultaneously with the hallucinatory and catatonic symptomatology induced by mescaline. The observations of Davis (11) are concordant with those of Chweitzer and coworkers (5) and of Walter (48). However interesting these similarities are, it is difficult to explain the correlation between the EEG changes induced by the hallucinogenic drugs and the psychotic-like symptomatology. In addition to diffuse cerebral electrographic modifications other effects of LSD on individual neuronal systems have been studied. Evarts and Marchall (16) have examined the effect of LSD on the post-synaptic potentials in the lateral geniculate body evoked by single shock stimulation of the optic nerve and found that the transmission in the geniculate was markedly depressed by LSD while the cortical response to stimulation of the optic radiation was not inhibited. Marrazzi (30) reported that both LSD and mescaline

depress the response of the optic cortex to transcallosal stimulation. This depression is attributed to synaptic inhibition which assigns the hallucinogenic drugs to the group of synaptic inhibitors. The central synaptic effects of LSD at varying doses on different neuronal systems have been studied by Purpura (36). He found first of all an initial facilitation with small amounts of LSD, followed by depression with larger ones. The dose levels for these effects varied with the type of synapse studied. For instance the facilitation was most prominent even with relatively large doses for the primary potential of the visual area, while cortical response to stimulation of cortico-cortical and transcallosal systems was inhibited at relatively low dose levels. The differences noted by Purpura between the effects of small and large doses of LSD can be correlated with our observations showing that the general pattern of cerebral electrographic activity was desynchronized with small doses of LSD while large doses of the same drug reverse this effect. At this point it is worth mentioning that very large doses of LSD do not produce an excited behavior in monkeys as small ones do, but instead produce sedation (45).

Purpura (36) reported that the recruiting cortical responses from stimulation of midline unspecific thalamic nuclei, after an initial facilitation, are inhibited by LSD. We know that the electrographic alerting and the recruiting responses are competitive, for it is impossible or difficult to evoke recruitment while an alerting effect is taking place (25). This competition is probably due to the fact that recruiting and alerting responses are mediated through the same diffuse thalamocortical system. For this reason one wonders whether the long lasting alert electrographic pattern produced by LSD could be responsible for the apparent inhibition of the recruiting responses.

We have observed that Frenquel can correct the electrographic changes evoked by LSD and by mescaline. This fact, together with the observations of Fabing (17) that Frenquel cures the psychotic manifestations following LSD administration, seems to indicate an apparent antagonism between the central action of the hallucinogenic drugs and Frenquel. Moreover there is some kind of specificity because Frenquel corrects the electrographic alertness induced by the hallucinogenic drugs but not by DFP, amphetamine or Meratran. Very puzzling is the lack of antagonism observed in our studies between Frenquel and Meratran because Frenquel is chemically related to Meratran, the first being alpha-4-piperidyl benzhydrol hydrochloride and the latter being alpha-2-piperidyl benzhydrol hydrochloride. The results of Brown and coworkers (4) showing that Frenquel can tranquilize animals rendered over-excited by Meratran cannot be explained by antagonistic effects on the MDAS.

In view of the fact that the administration of hallucinogenic drugs renders the MDAS functionally overactive, one would expect that the antagonizing action of Frenquel should be due to a depression of the same system. We observed (40), however, that Frenquel administered alone is not at all a depressant of that system. For this reason Frenquel does not correct conditions of lasting alertness produced by the other drugs.

While the action of Frenquel seems specific in antagonizing the hallucinogenic drug effects, other drugs, like atropine, barbiturates and probably Chlorpromazine, act non-specifically. These three drugs are depressants of the MDAS and correct an electrographic alertness no matter how produced, whether by the hallucinogenic agents or by any other means. This explains, for instance, the results of Gastaut and coworkers (22) who observed that the administration of thiopental could correct the electrographic LSD-induced changes. Since thiopental is a short-acting barbiturate these authors could also observe the reappearance of the LSD effect after that of thiopental had vanished.

A suggestion for the mechanism of action of Frenquel in correcting the electrographic effects of hallucinogens can be sought in recent pharmacological data on the mode of action of LSD. It was found by Gaddum and Hameed (21) that LSD antagonizes the action of serotonin on the rat uterus. This antagonism is of the type usually described as receptor blockade: LSD combines with the receptors of serotonin thereby blocking their reaction with serotonin. In our laboratory Costa (7) has

studied the effect of several drugs on the serotonin-induced contractions of the rat's uterus. He confirmed the observations of Gaddum and Hameed (21) that LSD inhibits serotonin, but he also demonstrated that LSD, in concentrations lower than the inhibiting ones, facilitates the action of serotonin. Costa (7) also found that mescaline, in pharmacologically significant concentrations, always augments the serotonin-induced uterine contractions, while Frenquel, as well as the other tranquilizing drugs Reserpine and Chlorpromazine, inhibits serotonin.

On the basis of these findings we may attribute the electrographic alerting effect of mescaline and of small doses of LSD to a serotonin-facilitating mechanism. An inhibition of serotonin can be held responsible for the ability of Frenquel and of large doses of LSD to correct the electrographic changes. This interpretation is entirely hypothetical because the importance of serotonin in the function of the central nervous system is yet undetermined. Proceeding on the assumption that serotonin plays a part in brain physiology (49), our suggestions lead to the working hypothesis that the psychotogenic effect of mescaline and LSD is due to serotonin-facilitating properties. The correction of LSD-induced psychosis by Frenquel and probably the beneficial effects of Frenquel, Reserpine and Chlorpromazine in clinical psychiatry could be partially due to their ability to inhibit serotonin.

Summary and Conclusions

1. A cerebral electrographic change, consisting in a long lasting alerting effect, follows the injection into rabbits of LSD in small amounts (1–15 gamma/kg.) and of mescaline. These findings correlate with EEG observations in psychotic patients and in volunteers under the action of LSD and mescaline.

2. Frenquel, which corrects the LSD-induced experimental psychoses, also eliminates the electrographic changes evoked by LSD and mescaline.

3. LSD in large amounts (20–60 gamma/kg.) has an effect on the cerebral electrical activity opposite to the one produced by small doses (1–15 gamma/kg.). This is correlated with the observation that LSD in very large quantities has a tranquilizing action.

4. These observations are tentatively explained on the basis of our pharmacological data and those of others. The production of electrographic alertness by the hallucinogenic drugs and their psychotogenic effect are attributed to a serotonin-facilitating property. The correction of the electrographic LSD- or mescaline-induced abnormalities by the use of Frenquel is attributed to the serotonin-inhibiting properties of that drug.

Bibliography

1. Abramson, H. A., Jarvik, M. E., Kaufman, M. R., Kornetsky, C., Levine, A., and Wagner, M.: Lysergic acid diethylamide (LSD-25): I. Physiological and perceptual responses. *J. Psychol., 39:* 3–60, 1955.
2. Beringer, K.: *Der Mezcalinrausch.* Berlin: Springer, 1927.
3. Bradley, P. B., Elkes, C., and Elkes, J.: On some effects of lysergic acid diethylamide (LSD 25) in normal volunteers. *J. Physiol., 121:* 50P–51P, 1953.
4. Brown, B. B., Feldman, R., and Braun, D. L.: Pharmacologic studies of an LSD antagonist, 4-piperidyl diphenyl carbinol hydrochloride. *Fed. Proc., 14:* 322, 1955.
5. Chweitzer, A., Geblewicz, E., and Liberson, W.: Étude de l'électroencephalogramme humain dans un cas d'intoxication mescalinique. *Annee psychol., 37:* 94–98, 1936.
6. Cohn, R.: The influence of emotion on the human electroencephalogram. *J. Nerv. & Ment. Dis., 104:* 351–357, 1946.
7. Costa, E.: Personal communication.
8. Condrau, G.: Klinische Erfahrungen aus Geisteskranken mit Lysergsäure-diäthylamid. *Acta Psychiat. et Neurol., 24:* 9–32, 1949.
9. Davis, P. A.: Electroencephalograms of manic-depressive patients. *Am. J. Psychiat., 98:* 430–433, 1940.
10. Davis, P. A.: Evaluation of the electroencephalograms of schizophrenic patients. *Am. J. Psychiat., 98:* 851–860, 1940.
11. Davis, P. A.: Comparative study of the EEG of schizophrenic and manic-depressive patients. *Am. J. Psychiat., 99:* 210–217, 1942.
12. De Giacomo, U.: Donnees biologiques sur l'action psychophysiologique de la diéthylamide de l'acide lysergique. International Congress of Psychiatry, Paris, 1950.
13. Delay, J., Lhermitte, F., Verdeaux, G., and Verdeaux, J.: Modifications de l'EEG du lapin par la diéthylamide de l'acide d-lysergique. *Rev. Neurol., 86:* 7–88, 1952.
14. Elkes, J., Elkes, C., and Bradley, P. B.: The effects of some drugs on the electrical activity of the brain and on behavior. *J. Ment. Sc., 100:* 125–128, 1954.
15. Ellingson, R. J.: The incidence of EEG abnormality among patients with mental disorders of apparently nonorganic origin: a critical review. *Am. J. Psychiat., 111:* 263–275, 1954.
16. Evarts, E. V., and Marshall, W. H.: Effects of lysergic acid diethylamide on excitability cycle of the lateral geniculate. Annual Meeting American Neurological Association, Chicago, 1955.

17. Fabing, H.: A new blocking agent against the development of LSD 25-induced psychosis. *Science, 121:* 208 1955.
18. Finley, K. H.: On the occurence of rapid frequency potential changes in the human electroencephalogram. *Am. J. Psychiat., 101:* 194–200, 1944.
19. Finley, K. H., and Campbell, G. M.: Electroencephalography in schizophrenia. *Am. J. Psychiat., 98:* 374–381, 1941.
20. Forrer, G. R., and Goldner, R. D.: Experimental physiological studies with lysergic acid diethylamide (LSD-25). *Arch. Neurol. & Psychiat., 65:* 581–588, 1951.
21. Gaddum, J. H., and Hameed, K. A.: Drugs which antagonize 5-hydroxytryptamine. *Brit. J. Pharmacol., 9:* 240–248, 1954.
22. Gastaut, H., Ferrer, S., and Castells, C.: Action de la diéthylamide de l'acide d-lysergique (LSD 25) sur les fonctions psychiques et l'électroencephalogramme. *Conf. Neurol., 13:* 102–120, 1953.
23. Hoch, P. H.: Experimentally produced psychoses. *Am. J. Psychiat., 107:* 607–611, 1951.
24. Jasper, H.: Diffuse projection system: the integrative action of the thalamic reticular system. *EEG Clin. Neurophysiol., 1:* 405–419, 1949.
25. Jasper, H., Naquet, R., and King, E.: Thalamocortical recruiting response in sensory receiving areas in cat. *EEG Clin. Neurophysiol., 7:* 99–114, 1955.
26. Kennard, M. A., and Levy, S.: The meaning of the abnormal electroencephalogram in schizophrenia. *J. Nerv. & Ment. Dis., 116:* 413–423, 1952.
27. Kennard, M. A., Rabinovitch, M. S., and Fister, W. P.: The use of a frequency analysis in the interpretation of the EEG's of patients with psychological disorders. *EEG Clin. Neurophysiol., 7:* 29–38, 1955.
28. Lemere, F.: The significance of individual differences in the Berger rhythm. *Brain, 59:* 366–375, 1936.
29. Lemere, F.: Cortical energy production in the psychoses. *Psychosom. Med., 3:* 152–156, 1941.
30. Marrazzi, A. S., and Hart, E. R.: The relation of hallucinogens to adrenergic cerebral neurohumors. *Science, 121:* 365–367, 1955.
31. Matefi, L.: Mescalin-und Lysergsäurediäthylamid-Rausch. *Conf. Neurol., 12:* 146–177, 1952.
32. Moruzzi, G., and Magoun, H. W.: Brainstem reticular formation and activation of the EEG. *EEG. Clin. Neurophysiol., 1:* 455–473, 1949.
33. Newman, H. W., and Lawrence, R.: The electroencephalogram in functional psychiatric disorders. *Stanford Med. Bull., 10:* 76–77, 1952.
34. Pennes, H. H.: Clinical reactions of schizophrenics to sodium amytal, pervitin hydrochloride, mescaline sulphate and d-lysergic acid diethylamide (LSD 25). *J. Nerv. & Ment. Dis., 119:* 95–112, 1954.
35. Pine, J., and Pine, H. M.: Clinical analysis of patients with low voltage EEG. *J. Nerv. & Ment. Dis., 117:* 191–198, 1953.
36. Purpura, D. P.: Electrophysiological analysis of the psychotogenic drug action on the evoked potentials of the cat's brain. Annual Meeting American Neurological Association, Chicago, 1955.
37. Rinaldi, Franco, and Himwich, H. E.: A comparison of effects of reserpine and some barbiturates on the electrical activity of cortical and subcortical structures of the brain of rabbits. *Ann. N. Y. Acad. Sc., 61:* 27–35, 1955.
38. Rinaldi, Franco, and Himwich, H. E.: Alerting responses and actions of atropine and cholinergic drugs. *Arch. Neurol. & Psychiat., 73:* 387–395, 1955.
39. Rinaldi, Franco, and Himwich, H. E.: Cholinergic mechanism involved in function of mesodiencephalic activating system. *Arch. Neurol. & Psychiat., 73:* 396–402, 1955.
40. Rinaldi, Franco, and Himwich, H. E.: Drugs affecting psychotic behavior and the function of the mesodiencephalic activating system. *Dis. Nerv. System, 16:* 133–141, 1955.
41. Rinaldi, Franco, Himwich, H. E., and Rudy, L.: A comparative study of Serpasil, Thorazine and MER-17. Annual Meeting of the American Psychiatric Association, Atlantic City, 1955.
42. Rinkel, M., De Shon, J., Hyde, R. W., and Solomon, H. C.: Experimental schizophrenia-like symptoms. *Am. J. Psychiat., 108:* 572–578, 1952.
43. Rubin, A., Malamud, W., and Hope, J. M.: The electroencephalogram and psychopathological manifestations in schizophrenia as influenced by drugs. *Psychosom. Med., 4:* 355–360, 1942.
44. Savage, C.: Lysergic acid diethylamide (LSD 25). *Am. J. Psychiat., 108:* 896–900, 1952.
45. Sebrell, W. H.: Chemistry in chronic disease research. *Chem. Engin. News, 33:* 1856–1860, 1955.
46. Sloane, B., and Lovett, J. W.: Psychophysiological investigations in experimental psychoses: result of the exhibition of d-lysergic acid diethylamide to psychiatric patients. *J. Ment. Sc., 100:* 129–144, 1954.
47. Stoll, W. A.: Lysergsäure-diäthylamid: ein Phantastikum aus der Mütterkorngruppe. *Schweiz. Arch. f. Neurol. u. Psychiat., 60:* 1–45, 1947.
48. Walter, W. G.: The technique and application of electroencephalography: critical review. *J. Neurol. Psychiat., 1:* 359–366, 1938.
49. Woolley, D. W., and Shaw, E.: Some neurophysiological aspects of serotonin. *Brit. M. J., 2:* 122–132, 1954.

THUDICHUM PSYCHIATRIC RESEARCH LABORATORY
GALESBURG STATE RESEARCH HOSPITAL
GALESBURG, ILLINOIS