Pharmacology Biochemistry & Behavior, Vol. 16, pp. 573–578, 1982. Printed in the U.S.A.

Effects of Marihuana Cannabinoids on Seizure Activity in Cobalt-Epileptic Rats[1]

BRENDA K. COLASANTI,[2] CHARLES LINDAMOOD, III[3]
AND CHARLES R. CRAIG

Department of Pharmacology and Toxicology
West Virginia University Medical Center, Morgantown, WV 26506

Received 6 November 1981

COLASANTI, B. K., C. LINDAMOOD, III AND C. R. CRAIG. *Effects of marihuana cannabinoids on seizure activity in cobalt-epileptic rats*. PHARMAC. BIOCHEM. BEHAV. **16**(4) 573–578, 1982.—Rats rendered chronically epileptic by bilateral implantation of cobalt into frontal cortices were simultaneously prepared with permanent electrodes for longitudinal recording of the electroencephalogram (EEG) and electromyogram (EMG). Delta-8-tetrahydrocannabinol (Δ-8-THC; 10 mg/kg), delta-9-tetrahydrocannabinol (Δ-9-THC; 10 mg/kg), cannabidiol (CBD; 60 mg/kg), or polyvinylpyrrolidone (PVP) vehicle (2 ml/kg) was administered IP twice daily from day 7 through 10 after cobalt implantation, at which time generalized seizure activity in non-treated cobalt-epileptic rats was maximal. Relative to PVP-treated controls, CBD did not alter the frequency of appearance of seizures during the course of repeated administration. In contrast, both Δ-8-THC and Δ-9-THC markedly reduced the incidence of seizures on the first and second days of administration. Interictal spiking during this period, on the other hand, was actually enhanced. On the third and fourth days, tolerance to the effect on seizures was evident, with a return of seizure frequency of THC-treated rats to values not significantly different from those of controls. Unlike the effect on seizures, no tolerance developed to the marked suppression of rapid eye movement (REM) sleep induces by Δ-8-THC and Δ-9-THC. REM sleep remained reduced in the treated animals during the first 2 days after termination of THC administration. In contrast, REM sleep time was unaffected by repeated administration of CBD. These results suggest that Δ-8-THC and Δ-9-THC exert their initial anticonvulsant effect by limiting the spread of epileptogenic activity originating from the cobalt focus.

Tetrahydrocannabinols Cannabidiol Cobalt epilepsy Seizures REM sleep

THE anticonvulsant potential of the tetrahydrocannabinols and cannabidiol has received considerable attention in recent years [9,24]. These marihuana cannabinoids resemble phenytoin with regard to their effects on acute seizure activity. Both compounds afford protection of animals against maximal seizures induced by electroshock but fail to alleviate minimal seizures induced by pentylenetetrazol.

Anticonvulsant effectiveness of the cannabinoids has also been evaluated in various chronic models of epilepsy. Delta-9-tetrahydrocannabinol (Δ-9-THC), the major psychoactive constituent of marihuana [26], exerted anticonvulsant activity in epileptic gerbils [12], epileptic chickens [22], and amygdaloid-kindled rats [10, 11, 20]. Anticonvulsant activity of Δ-9-THC in the epileptic baboon *Papio papio* has been somewhat variable, with some researchers observing reduction of photomyoclonic seizure frequency [25] and others no change [27,32]. On the other hand, this cannabinoid actually exacerbated seizures in epileptic beagles and enhanced epileptiform spiking activity in cats with alumina cream motor foci [18]. In contrast to Δ-9-THC, cannabidiol (CBD), a marihuana cannabinoid devoid of both psychic and cardiovascular effects [29], did not increase convulsive activity in epileptic beagles [18]. CBD was likewise ineffective in protecting epileptic gerbils against seizures occurring spontaneously [12].

In the present study, the effects of repeated cannabinoid administration on seizure phenomena accompanying cobalt experimental epilepsy in the rat have been examined. Utilization of this chronic model of epilepsy has allowed assessment of changes in the occurrence of both abnormal focal electrical activity and generalized major motor seizures [8,13]. Cannabinoid effects on the rapid eye movement (REM) phase of sleep have also been delineated.

METHOD

A total of 25 adult male Sprague-Dawley rats weighing 150–250 g were used in these experiments. With the animals under anesthesia induced by subcutaneous administration of 0.4 cc Innovar® (a commercial mixture containing 0.05 mg

[1]Supported in part by Biomedical Research Support Grant S07 RR05433 17, by the West Virginia University Medical Corporation, and by the National Institute of General Medical Sciences Training Grant 5-T 32 GM 07039.

[2]Reprint requests should be sent to Dr. Brenda K. Colasanti, Department of Pharmacology and Toxicology, West Virginia University Medical Center, Morgantown, WV 26506.

[3]Present address: CIIT, Research Triangle Park, NC 27709.

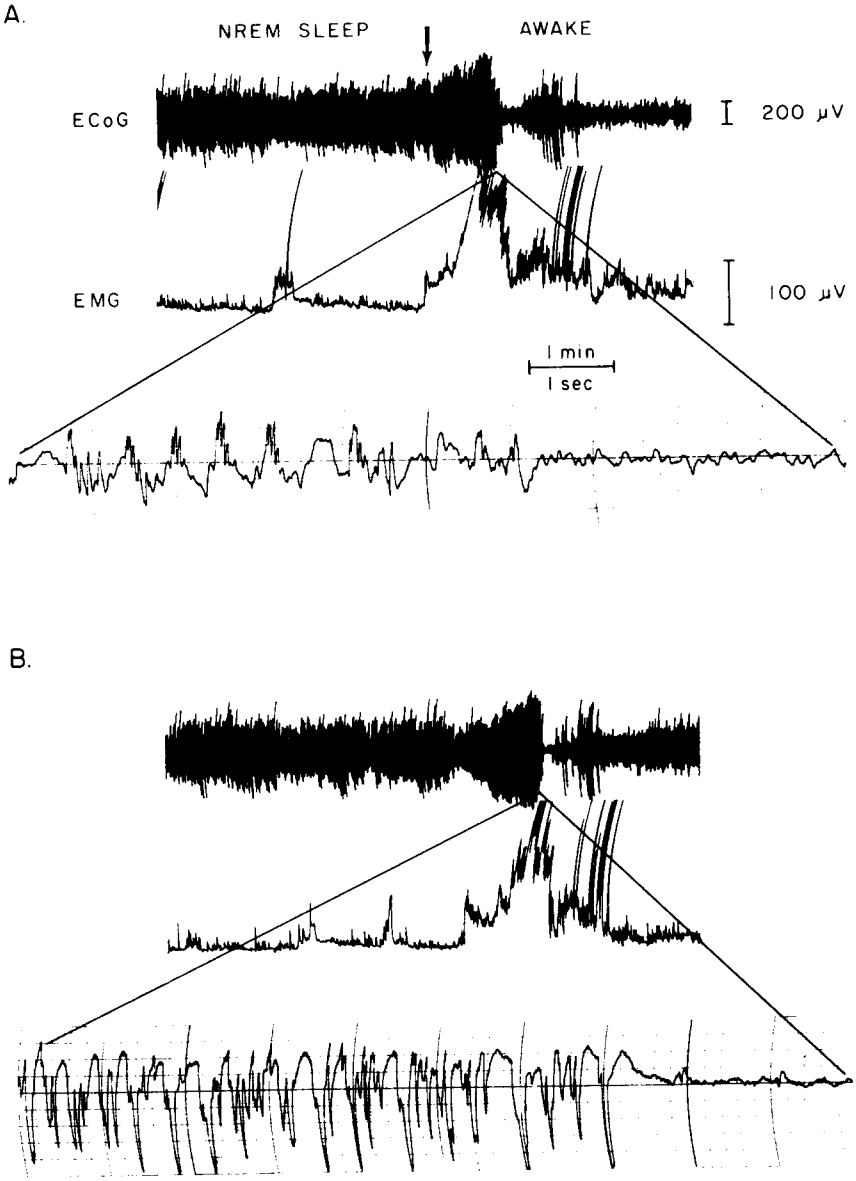

FIG. 1. A. ECoG and EMG recordings collected from a representative rat during the appearance of a seizure with incomplete secondary generalization. B. ECoG and EMG tracings recorded during the appearance of a completely generalized seizure. Note the electrical silence after its termination.

fentanyl and 2.5 mg dehydrobenzperidol per ml), 2 to 4 mm^2 areas of skull lying 2 mm to the right and left of the midline and 2 mm anterior to the bregma were removed. The dura was reflected, and 1 to 2 mm lengths of cobalt wire 1 mm in diameter (Kulite Tungsten Co., Ridgefield, NJ) were inserted directly into both right and left cerebral cortices. For bipolar recording of the cortical EEG (ECoG), stainless steel screws were engaged in the skull over the frontal and parietal cortices. Electrode placements were 4 mm anterior and 3 mm posterior to the bregma. All electrodes were placed 2 mm lateral to the midline. For bipolar recording of the electromyogram (EMG), stainless steel wires were sutured deeply into the temporalis muscles. Electrodes were soldered to a 7-pin Amphenol connector which was positioned over the skull with acrylic dental cement.

A total of 20 animals were prepared with indwelling intraperitoneal cannulas for drug administration at the time of electrode implantation. The cannulas were constructed by fusion of polyethylene 50 (PE 50) and silastic tubing. The latter end of the cannula was inserted into the peritoneal cavity and held in place with a suture. The PE 50 portion was threaded subcutaneously to the scapulae, where it exited through the skin via a puncture wound.

After completion of all surgical procedures, the rats were placed in individual recording cages and connected to a cable. The EEG and EMG activities of these unrestrained and

TABLE 1

SEIZURE FREQUENCY IN PVP-TREATED* AND NON-TREATED RATS DURING COBALT EXPERIMENTAL EPILEPSY

Time After Cobalt Placement (Days)	Seizure Frequency (number of seizures ± S.E.M.) Non-treated	PVP-treated
5–6	21.0 ± 1.7	24.6 ± 7.0
7–8	23.8 ± 8.2	26.9 ± 5.7
9–10	19.2 ± 9.7	17.7 ± 6.4
11–12	10.0 ± 5.4	12.5 ± 7.0

*PVP administered IP twice daily from days 7 through 10 after cobalt placement.

freely moving animals were recorded continuously over 24-hour periods on an 8-channel Grass model 7 polygraph from days 5 through 12 post-surgery. To reduce the volume of chart paper accumulated. the EEG was usually recorded at the slow chart speed of 25 mm/min.

Δ-9-THC and Δ-8-THC, both dissolved in ethanol, and CBD crystals were obtained courtesy of the National Institute on Drug Abuse. The cannabinoids were suspended in polyvinylpyrrolidone-40 (PVP; Sigma Chemical Company, St. Louis, MO) using a modification of the procedure of Fenimore and Loy [19]. Ethanolic solutions of cannabinoids were mixed with ethanolic solutions of PVP such that the mixture contained a ratio of PVP/cannabinoid (mg/mg) that was 20/1 for Δ-9- and Δ-8-THC and 7/1 for CBD. The ethanol was evaporated under reduced pressure and the cannabinoid-PVP complex washed from the flask with saline. Stock solutions of cannabinoid containing 5 mg Δ-9- or Δ-8-THC/ml PVP-saline and 30 mg CBD/ml PVP-saline were prepared fresh one day prior to use.

Δ-8-THC (10 mg/kg), Δ-9-THC (10 mg/kg), CBD (60 mg/kg) or PVP vehicle was administered via the indwelling IP cannulas twice daily (8:00 a.m. and 4:00 p.m.) to groups of 5 rats on days 7 through 10 after cobalt implantation. The injection volume was 2 ml/kg. Another group of 5 rats received no drug or vehicle treatment.

Generalized motor seizures were quantified on the basis of the accompanying ECoG and behavioral manifestations [8]. The electrographic criterion used for detecting seizure activity was the appearance of repetitive, bilaterally hypersynchronous spike activity in all cortical leads. Behaviorally, clonic and tonic movements of both forelimbs and of the facial muscles accompanied all seizures. Hindlimb musculature was additionally involved in those seizures terminated electrically by pronounced ECoG flattening.

REM sleep time was determined by evaluation of the ECoG activity in conjunction with the EMG tracings. REM sleep episodes were identified by the appearance of low voltage fast ECoG activity resembling wakefulness but occurring in association with extreme reduction of the EMG activity surpassing that of slow wave sleep. Room lighting conditions were timer-regulated to provide a 12-hour light-dark cycle.

Statistical comparisons between results for PVP-treated and cannabinoid-treated cobalt-epileptic rats were made by Student's 2-tailed t-test. The 5% probability level was taken as the lower limit of significance.

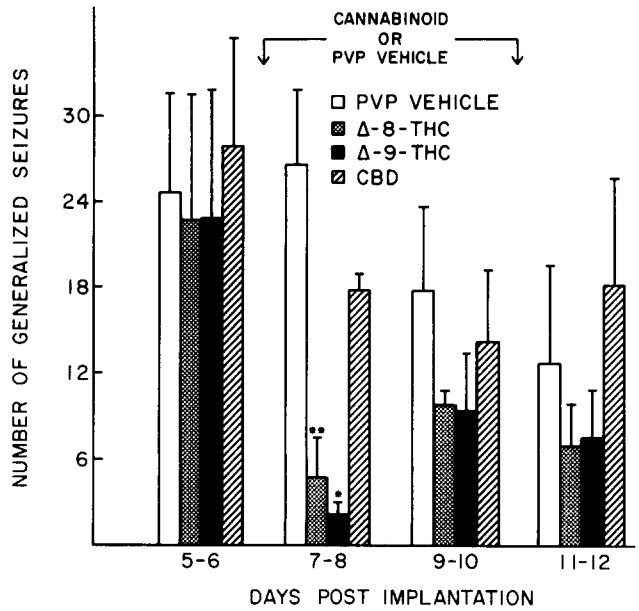

FIG. 2. Effects of marihuana cannabinoids on seizure frequency in rats with cobalt implanted bilaterally in frontal cortices. Δ-8-THC (20 mg/kg/day), Δ-9-THC (20 mg/kg/day), CBD (120 mg/kg/day) or PVP vehicle was injected IP via a chronic indwelling polyethylene cannula on days 7 through 10 post-implantation. Each vertical bar represents the mean±S.E. for 5 rats. *$p<0.05$, **$p<0.02$.

RESULTS

By the fourth to fifth day after bilateral cerebral cobalt implantation, focal seizures with incomplete secondary generalization (Fig. 1A) appeared in the ECoG recordings of the five experimental animals not subjected to drug or vehicle administration. In the next few days, completely generalized seizures (Fig. 1B), also of focal origin, appeared in the ECoG tracings as well, and from days six to ten after surgery seizure activity of both types was maximal. After this time, seizure frequency began to decline. Seizure incidence from days 7 through 10 after cobalt placement was not affected by administration of the PVP vehicle (Table 1).

During the first two days of treatment with Δ-8-THC or Δ-9-THC at a dose of 10 mg/kg IP twice daily, the incidence of generalized seizure activity in the cobalt-epileptic rats was markedly less than that occurring in animals treated with the PVP vehicle only during the same two days (Fig. 2). The effects of the first few injections of these cannabinoids in rats with high seizure frequencies were dramatic. Within 15 to 30 minutes after administration, generalized seizure activity was completely abolished (Fig. 3). By the third treatment day, however, tolerance development to the anticonvulsant activity became evident, with a return of seizure frequency during the third and fourth days to values approaching those of the PVP controls during the same days (Fig. 2). The number of seizures occurring within the first two days after cessation of Δ-8- or Δ-9-THC administration did not significantly differ from that for the PVP controls. In contrast with results for THC, administration of CBD at a dose of 60 mg/kg IP twice daily had no effect on the appearance of generalized seizure activity throughout the four-day period of treatment (Fig. 2).

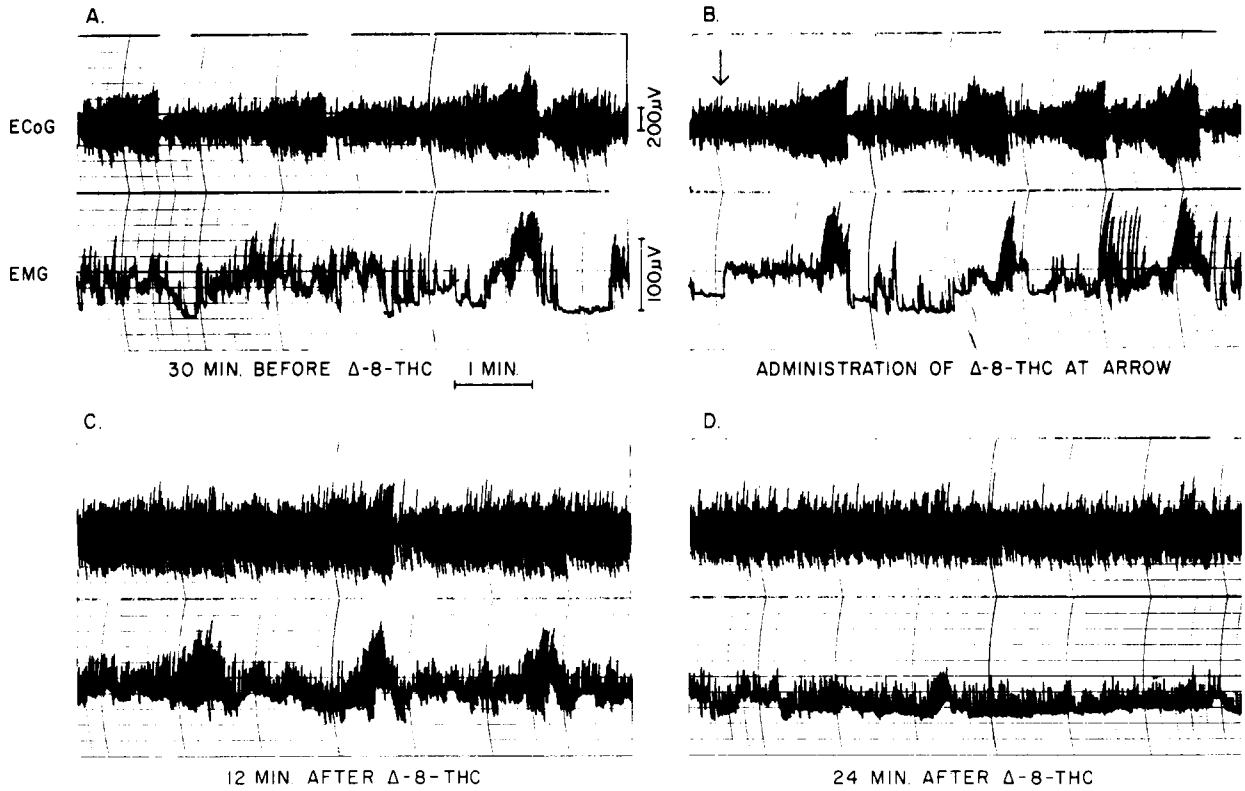

FIG. 3. ECoG and EMG tracings illustrating the immediate effect of Δ-8-THC on generalized motor seizures during cobalt experimental epilepsy in the rat. Before drug administration (Panel A), seizures were occurring every several minutes. Within 15 to 20 minutes after administration of Δ-8-THC, 10 mg/kg IP, generalized seizure activity was completely abolished.

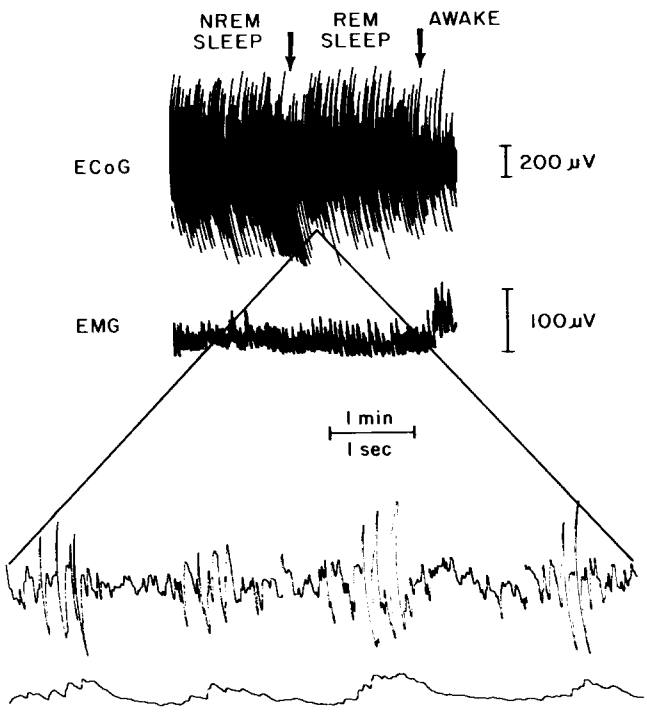

FIG. 4. Polygraphic tracings collected during the period in which spikes and spike and wave complexes appeared continuously in the ECoG of a cobalt-epileptic rat treated with the PVP vehicle.

TABLE 2

EFFECTS OF CANNABINOIDS ON THE APPEARANCE OF ECoG POLYSPIKES DURING COBALT EXPERIMENTAL EPILEPSY IN THE RAT

Treatment	Duration Polyspike Periods (hr ± S.E.M.; n=5)
PVP Vehicle	23.4 ± 3.4
Δ-9-THC (20 mg/kg/day)	69.5 ± 14.9*
Δ-8-THC (20 mg/kg/day)	52.8 ± 9.7*
CBD (120 mg/kg/day)	35.5 ± 6.4

*$p<0.001$ in comparison with value for PVP vehicle.

Between 6 and 12 days after cobalt implantation, spikes and spike and wave complexes accompanied behaviorally by unilateral clonic movements of the facial and forelimb musculature began to appear in the ECoG during wakefulness. This type of focal activity subsequently prevailed during slow wave sleep and REM sleep as well (Fig. 4) and persisted in the PVP control rats for almost 24 hours. The duration of appearance of polyspikes with a behavioral counterpart was significantly prolonged by treatment with either Δ-8-THC or Δ-9-THC (Table 2). CBD, on the other hand, did not significantly alter the duration of this epileptiform activity.

Repeated administration of Δ-8- or Δ-9-THC resulted in a marked suppression of REM sleep during all four days of treatment (Fig. 5). REM sleep time remained greatly reduced

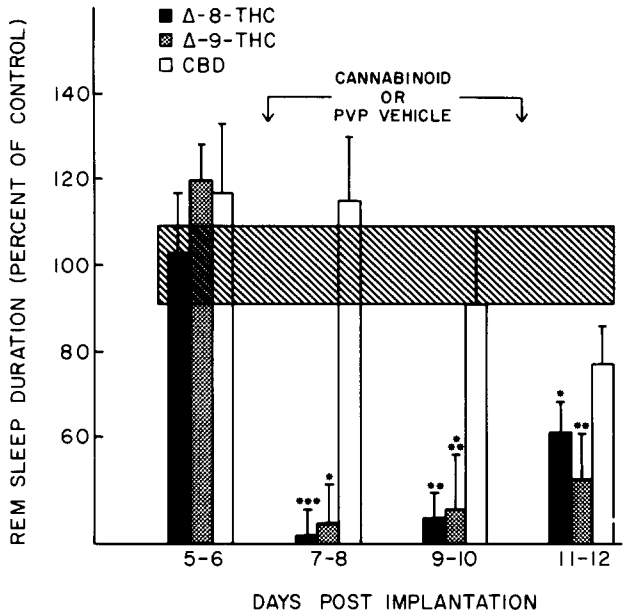

FIG. 5. Effects of marihuana cannabinoids on REM sleep time in cobalt-epileptic rats. Δ-8-THC (20 mg/kg/day), Δ-9-THC (20 mg/kg/day), CBD (120 mg/kg/day) or PVP vehicle was administered IP via a chronic indwelling polyethylene cannula on days 7 through 10 after cobalt implantation. Hatched area represents ± 1 standard error for REM sleep values of PVP-treated control rats. Control values (minutes per 24 hrs) were 58.8±7.2, days 5 and 6; 56.8±8.2, days 7 and 8; 66±8.0, days 9 and 10; and 88.4±11.2, days 11 and 12. *$p<0.05$; **$p<0.02$; ***$p<0.001$.

during the first two days after termination of THC administration. Repeated administration of CBD had no effect on the appearance of REM sleep episodes (Fig. 5). Values for REM sleep time of PVP-treated rats during days 7 through 10 after surgery were not significantly different from those for untreated cobalt-epileptic animals during the same days (Table 3).

TABLE 3

REM SLEEP DURATION IN PVP-TREATED*AND NON-TREATED RATS DURING COBALT EXPERIMENTAL EPILEPSY

Time After Cobalt Placement (Days)	REM Sleep Time (minutes per 24 hr ± S.E.M.) Non-treated	PVP-treated
5–6	63.3 ± 7.2	58.8 ± 7.2
7–8	50.1 ± 10.2	56.8 ± 8.2
9–10	63.5 ± 9.2	66.0 ± 8.0
11–12	73.8 ± 5.4	88.4 ± 11.2

*PVP administered IP twice daily from days 7 through 10 after cobalt placement.

DISCUSSION

The results of this study have demonstrated that both Δ-8-THC and Δ-9-THC exert anticonvulsant activity in rats exhibiting spontaneous generalized seizures during cobalt experimental epilepsy. Activity of the cobalt focus, on the other hand, was actually enhanced by these two psychoactive marihuana cannabinoids. This latter effect of THC was also recently observed by others in acute experiments [3]. Phenobarbital, which is widely used clinically as an anticonvulsant, likewise enhances focal activity in cobalt-epileptic rats [15] as well as in man.

In contrast with results for the THC cannabinoids, repeated administration of CBD had no effect on either seizure incidence or the frequency of focal polyspikes with a behavioral counterpart. In this regard, CBD resembles phenytoin, which has previously been reported to exert no effect on the abnormal focal activity [15] or generalized motor seizures [13] accompanying cobalt experimental epilepsy in the rat. Other similarities between CBD and phenytoin have previously been observed. Like phenytoin, CBD reduces posttetanic potentiation [21,31] but exerts no effect on photically evoked afterdischarge potentials [30].

Our results provide further evidence that Δ-9-THC displays an anticonvulsant spectrum of activity distinct from that of CBD. Because Δ-8- and Δ-9-THC activate the cobalt focus but inhibit the subsequent appearance of generalized seizure activity, one can infer that these cannabinoids exert their anticonvulsant effect by limiting seizure spread. The mechanism by which THC suppresses seizure spread remains to be defined. Phenytoin is thought to limit seizure spread by reducing posttetanic potentiation [16], and CBD, which also reduces posttetanic potentiation [21], may presumably act similarly. However, although metabolites of Δ-9-THC reduce posttetanic potentiation, Δ-9-THC itself does not [31]. Elucidation of the mechanism whereby Δ-9-THC reduces seizure spread should lead to innovations in anticonvulsant therapy.

By the third day of repeated administration to the cobalt-epileptic rats, Δ-8- and Δ-9-THC were much less effective in reducing seizure occurrence. Rapid development of tolerance to the anticonvulsant effect of Δ-9-THC has also been reported to occur in amygdaloid-kindled rats [11,20], rats subjected to maximal electroshock [23], and seizure-susceptible gerbils [12]. However, tolerance also developed rapidly to the anticonvulsant effects of phenytoin and phenobarbital in rats subjected to electroshock [23]. Because tolerance to the anticonvulsant effect of the latter two drugs is not observed clinically [2], it has been suggested that only clinical studies can determine the significance of this effect [23].

The marked suppression of REM sleep induced by Δ-8-THC and Δ-9-THC in the cobalt-epileptic rats was much greater than that reported previously for normal rats given comparable doses [28]. Pentylenetetrazol and phenytoin have likewise been found to produce a greater reduction of REM sleep time in cobalt-epileptic rats than in normal animals [7,14]. A relationship between sleep and seizure activity has been well documented in experimental animals [4,5,6] as well as in man [1]. It appears that the REM stage of sleep in rats rendered chronically epileptic by cerebral cobalt implantation is highly susceptible to disruption by several classes of centrally acting drugs. Whether human epileptics are similarly affected remains to be determined.

In a survey concerning marihuana usage among human epileptics, it was found that a substantial number of patients abuse marihuana without obvious effects on their condition [17]. However, one epileptic reported that marihuana usage exacerbated his seizures while another reported that smok-

ing marihuana actually improved his condition. In animal studies, likewise, both enhancement [18] and alleviation [10, 12, 22] of seizure activity have been observed. The results of the present study may help to explain these divergent effects of marihuana. While the psychoactive cannabinoids, Δ-8-THC and Δ-9-THC, markedly reduce the appearance of generalized seizures, activity of the epileptogenic focus is actually enhanced. Of the variety of forms of epilepsies encountered clinically, some may be aggravated by stimulation of active foci while others may be alleviated by inhibition of seizure spread.

REFERENCES

1. Batini, C., A. Criticos, J. Fressy and H. Gastaut. Nocturnal sleep in patients presenting epilepsy with bisynchronous EEG discharges. *Electroenceph. clin. Neurophysiol.* **14:** 957–958, 1962.
2. Buchthal, F. and M. A. Lennox-Buchthal. Relation of anticonvulsant effect to concentration in serum. In: *Antiepileptic Drugs,* edited by D. M. Woodbury, J. K. Penry and R. P. Schmidt. New York: Raven Press, 1972, p. 198.
3. Chiu, P., D. M. Olsen, H. K. Borys, R. Karler and S. K. Turkanis. The influence of cannabidiol and Δ-9-tetrahydrocannabinol on cobalt epilepsy in rats. *Epilepsia* **20:** 365–375, 1979.
4. Chocholova, L. and T. Radil-Weiss. Focal epileptoid EEG activity in rats in relationship to the level of vigilance. *Activitas nerv. sup.* **11:** 242–246, 1969.
5. Cohen, H. B. and W. C. Dement. Sleep: changes in threshold to electroconvulsive shock in rats after deprivation of "paradoxical" phase. *Science* **150:** 1318–1319, 1965.
6. Cohen, H. B. and W. C. Dement. Sleep: suppression of rapid eye movement phase in the cat after electroconvulsive shock. *Science* **154:** 396–398, 1966.
7. Colasanti, B. K., C. R. Craig and E. R. Hartman. Differential effects of pentylenetetrazol on REM sleep in naive and cobalt-epileptic rats. *Psychopharmacologia* **37:** 151–157, 1974.
8. Colasanti, B. K., E. R. Hartman and C. R. Craig. Electrocorticogram and behavioral correlates during the development of chronic cobalt experimental epilepsy in the rat. *Epilepsia* **15:** 361–373, 1974.
9. Consroe, P., B. Jones, H. Laird and J. Reinking. Anticonvulsant-convulsant effects of delta-9-tetrahydrocannabinol. In: *Potential of Marihuana,* edited by S. Cohen and R. C. Stillman. New York: Plenum Medical Books, 1976, pp. 363–381.
10. Corcoran, M. E., J. A. McCaughran and J. A. Wada. Acute antiepileptic effects of Δ-9-tetrahydrocannabinol in rats with kindled seizures. *Expl Neurol.* **40:** 471–483, 1973.
11. Corcoran, M. E., J. A. McCaughran and J. A. Wada. Antiepileptic and prophylactic effects of tetrahydrocannabinols in amygdaloid kindled rats. *Epilepsia* **19:** 47–55, 1978.
12. Cox, B., M. Hamten, W. J. Loskota and P. Lomax. The anticonvulsant activity of cannabinoids in seizure sensitive gerbils. *Proc. west. Pharmac. Soc.* **18:** 154–157, 1975.
13. Craig, C. R., P. Chiu and B. K. Colasanti. Effects of diphenylhydantoin and trimethadione on seizure activity during cobalt experimental epilepsy in the rat. *Neuropharmacology* **15:** 485–489, 1976.
14. Craig, C. R. and B. K. Colasanti. The effect of prolonged administration of phenytoin on REM sleep time in naive and cobalt-epileptic rats. *Abstracts of the 7th International Congress on Pharmacology,* Paris, France, 1978, p. 817.
15. Dow, R. C., J. C. Forfar and J. K. McQueen. The effects of some anticonvulsant drugs on cobalt-induced epilepsy. *Epilepsia* **14:** 203–212, 1973.
16. Esplin, D. W. Effects of diphenylhydantoin on synaptic transmission in cat spinal cord and stellate ganglion. *J. Pharmac. exp. Ther.* **120:** 301–323, 1957.
17. Feeney, D. M. Marihuana use among epileptics. *J. Am. Med. Ass.* **235:** 1105, 1976.
18. Feeney, D. M., M. Spiker and G. K. Weiss. Marihuana and epilepsy: activation of symptoms by delta-9-THC. In: *The Therapeutic Potential of Marihuana,* edited by S. Cohen and R. C. Stillman. New York: Plenum Medical Books, 1976, pp. 343–362.
19. Fenimore, D. C. and P. R. Loy. Injectible dispersion of Δ-9-tetrahydrocannabinol in saline using polyvinylpyrrolidone. *J. Pharm. Pharmac.* **23:** 310, 1971.
20. Fried, P. A. and D. C. McIntyre. Electrical and behavioral attenuation of the anti-convulsant properties of delta-9-THC following chronic administration. *Psychopharmacologia* **31:** 215–227, 1973.
21. Izquierdo, I. and A. G. Nasello. Effects of cannabidiol and diphenylhydantoin on the hippocampus and on learning. *Psychopharmacologia* **31:** 167–175, 1973.
22. Johnson, D. D., J. R. McNeil, R. D. Crawford and W. C. Wilcox. Epileptiform seizures in domestic fowl. V. The anticonvulsant activity of delta-9-tetrahydrocannabinol. *Can. J. Physiol. Pharmac.* **53:** 1007–1013, 1975.
23. Karler, R., W. Cely and S. A. Turkanis. A study of the development of tolerance to an anticonvulsant effect of Δ-9-tetrahydrocannabinol and cannabidiol. *Res. Communs chem. Pathol. Pharmac.* **9:** 23–39, 1974.
24. Karler, R. and S. A. Turkanis. The antiepileptic potential of the cannabinoids. In: *The Therapeutic Potential of Marihuana,* edited by S. Cohen and R. C. Stillman. New York: Plenum Medical Books, 1976, pp. 383–397.
25. Killam, K. F. and E. K. Killam. The action of tetrahydrocannabinol on EEG and photomyoclonic seizures in the baboon. *Abstracts of the 5th International Congress on Pharmacology,* San Francisco, 1972, p. 124.
26. Mechoulam, R. Chemical basis of hasish activity. *Science* **169:** 611–612, 1970.
27. Meldrum, B. S., R. G. Fariello, E. A. Puil, M. Derouaux and R. Naquet. Delta-9-tetrahydrocannabinol and epilepsy in the photosensitive baboon, *Papio papio. Epilepsia* **15:** 255–264, 1974.
28. Moreton, J. E. and W. M. Davis. Effects of Δ^9-tetrahydrocannabinol on locomotor activity and on phases of sleep. *Pharmacologist* **12:** 258, 1970.
29. Perez-Reyes, M., M. C. Timmons and K. H. Davis. A comparison of the pharmacological activity in man of intravenously administered delta-9-THC, cannabinol and cannabidiol. *Experientia* **29:** 1368–1369, 1973.
30. Turkanis, S. A., P. Chiu, H. K. Borys and R. Karler. Influence of Δ-9-tetrahydrocannabinol and cannabidiol on photically evoked afterdischarge potentials. *Psychopharmacologia* **52:** 207–212, 1977.
31. Turkanis, S. A. and R. Karler. Influence of anticonvulsant cannabinoids on posttetanic potentiation at the isolated bullfrog ganglia. *Life Sci.* **17:** 569–578, 1975.
32. Wada, J. A., T. Osawa and M. E. Corcoran. Effects of tetrahydrocannabinols on kindled amygdaloid seizures and photogenic seizures in Senegalese baboons. *Papio papio. Epilepsia* **16:** 439–448, 1975.