THE INFLUENCE OF CANNABIDIOL AND Δ^9- TETRAHYDROCANNABINOL ON COBALT EPILEPSY IN RATS

by

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ABSTRACT

The mechanisms of the anticonvulsant activity of cannabidiol (CBD) and the central excitation of Δ^9-tetrahydrocannabinol (Δ^9-THC) were investigated electrophysiologically with conscious, unrestrained cobalt epileptic rats. The well-known antiepileptics, trimethadione, ethosuximide and phenytoin, were included as reference drugs. Direct measurements were made of spontaneously firing, epileptic potentials from a primary focus on the parietal cortex and convulsions were monitored visually. Ethosuximide and trimethadione decreased the frequency of focal potentials, but phenytoin and CBD exerted no such effect. Although CBD did not suppress the focal abnormality, it abolished jaw and limb clonus. Consequently, CBD may produce its anticonvulsant effect by depressing seizure spread in the CNS. In contrast, Δ^9-THC markedly increased the frequency of focal potentials, evoked generalized bursts of polyspikes and produced frank convulsions. 11-OH-Δ^9-THC, the major metabolite of Δ^9-THC displayed only one of the excitatory properties of the parent compound: production

of bursts of polyspikes. In contrast to Δ^9-THC and its 11-OH-metabolite, CBD, even in very high doses, did not induce any excitatory effects or convulsions. The present study provides the first evidence that CBD exerts anticonvulsant activity against the motor manifestations of a focal epilepsy, and that the mechanism of the effect may involve a depression of seizure spread in the CNS.

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I wish to dedicate this thesis to my parents and my brother, whose love and encouragement have supported me throughout my training.

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TABLE OF CONTENTS

INTRODUCTION

Both Δ^9-tetrahydrocannabinol (Δ^9-THC) and cannabidiol (CBD) have anticonvulsant activity (Garriott et al., 1968; Izquierdo and Tannhauser, 1973; Karler et al., 1973, 1974b,c,d; Karler and Turkanis, 1976a,b; Consroe et al., 1976), but Δ^9-THC is more toxic than CBD (Hollister, 1973; Perez-Reyes et al., 1973; Karler et al., 1974a, d). The potential toxicity of Δ^9-THC derives not only from its psychic and cardiovascular effects in humans, but also from its CNS depressant and excitatory properties in animals. The CNS depressant effect, which has been described in terms of motor toxicity, is important in defining the selectivity of the anticonvulsant activity relative to the neurotoxic activity (Karler et al., 1974a,d). The excitatory properties may be significant in relation to the illicit use of marihuana by epileptics, for there is a possibility that excitatory effects may exacerbate epilepsy (Keeler and Reifler, 1967). Because CBD does not have either the psycho- and/or cardiotoxicity of Δ^9-THC, and is a relatively more selective anticonvulsant than Δ^9-THC, CBD has been proposed as a potentially

useful antiepileptic (Karler and Turkanis, 1976a). Furthermore, CBD appears to lack most, if not all, the excitatory liabilities of Δ^9-THC (Karler et al., 1974d; Turkanis et al., 1974, 1977; Martin and Consroe, 1976; Feeney et al., 1976; Smiley et al., 1978).

Although both the anticonvulsant properties of CBD and the excitatory properties of Δ^9-THC have been recognized in a variety of test systems, only a few investigations have addressed the question of mechanism of action, (Corcoran et al., 1973; Izquierdo and Orsingher, 1973; Wada et al., 1975; Turkanis and Karler,1975, 1976). In the present work, the cobalt epilepsy model was selected for study because it provides a rapidly developing, reproducible, spontaneously firing, discrete focus that develops characteristic epileptic potentials in the electrocorticogram (Dow et al., 1962; Colasanti et al., 1974). The preparation permits the direct measurement from a primary focus of spontaneously firing epileptic potentials in unrestrained, conscious animals. Measurements from the cobalt-induced focus permit a study of the electrophysiological mechanisms of both the excitatory and anticonvulsant effects of the cannabinoids.

METHODS

Experimental Animals

The studies were carried out with male Sprague-Dawley rats (140-170 gm). In order to mount permanent stainless-steel screw electrodes (0-80, 1.6 mm, Plastic Products, Roanoke, Virginia) in the cranium, the animals were anesthetized with sodium pentobarbital (35-40 mg/kg administered intraperitoneally). Recording electrodes were stereotaxically positioned over both frontal cortices (3 mm anterior to bregma and 3 mm lateral to the midline) and over both parietal cortices (3 mm posterior to bregma and 3 mm lateral to the midline). In addition, two electrically connected reference-ground screw electrodes were inserted in the cranium: one over the cerebellum and the other over a frontal sinus. All electrodes were attached to a multipin Amphenol connector and dental acrylic was used to fasten the connector to the head, to insulate the electrodes electrically, and to form a conventional pedestal on each rat's head.

To induce an epileptic focus, a piece of cobalt wire, 1 mm in diameter and 1.5 mm in length, was positioned on the dura at the

time of electrode implantation (Colasanti et al., 1974). The cobalt-induced focus subsequently developed within 6-12 days. Control animals were prepared in a similar manner, except that the cobalt wire was omitted.

Experimental Procedures and Equipment

The experiments were carried out 6-19 days after cobalt implantation; in the present study, focal epileptic potential frequency during pre-drug control periods had a mean and standard deviation of 27 $\pm$ 8 potentials/min. In order for a potential to be classified as a cobalt-caused epileptic response, it had to exhibit clearly recognizable shapes, as depicted in Fig. 3, and in general it had to have an amplitude at least 2.5-fold greater than that of the background electrocorticogram. In support of these criteria for potential selection, the large amplitude potentials were readily abolished by ethosuximide (Figs. 1 and 2), as described by Dow et al. (1973) and Scuvee-Moreau et al. (1977). Some of the epileptic rats also exhibited jaw and limb clonus; such clonic activity was visually monitored throughout each experiment.

During an experiment, the rat was unanesthetized, awake and unrestrained and placed in a clear acrylic cage (20 x 32 x 32 cm), which was kept within a shielded recording chamber. The electrocorticograms were recorded differentially against a grounded reference electrode by high impedance capacitance-coupled preamplifiers and

a polygraph (Grass Instrument Company, model 5). Although electrical activity was measured from each frontal and parietal electrode simultaneously, in the present study, focal epileptic activity was directly recorded from a primary focus, which developed at the site of cobalt implantation in the left parietal cortex. Independent foci in the contralateral cortex rarely occurred and rats with such foci were excluded.

Drug Preparations

Ultrasound was used to disperse Δ^9-THC, 11-OH-Δ^9-THC, CBD and phenytoin in isotonic saline solution with Tween 80, as previously described (Turkanis et al., 1974). Trimethadione, ethosuximide and pentylenetetrazol (PTZ) were dissolved in an isotonic saline-Tween 80 solution; all drug and vehicle preparations contained a final concentration of 3% Tween 80 and were administered intraperitoneally. The injection volume, except for trimethadione and ethosuximide, was 0.1 ml/100 g body wt; in the trimethadione and ethosuximide experiments 0.2 ml/100 g body wt was used. Each animal was subjected to only one drug experiment in order to avoid the potential complications of drug interactions.

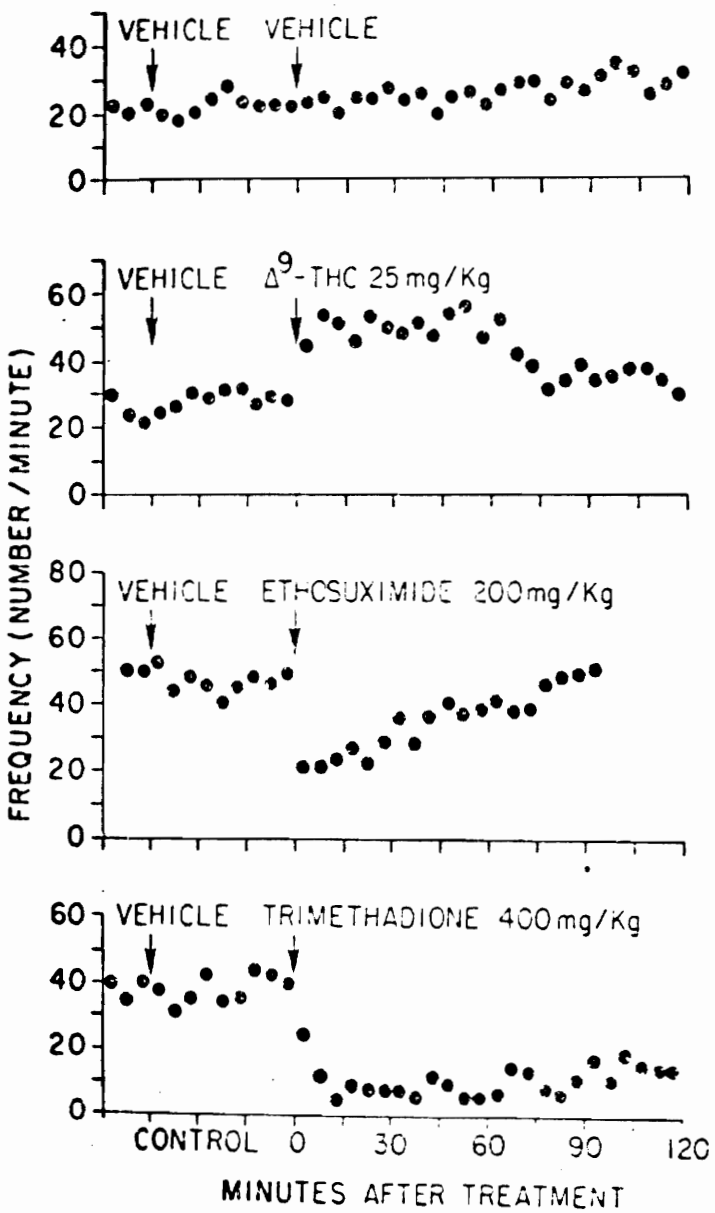
RESULTS

Time-effect Relations

The present study is an investigation of the influence of CBD and Δ^9-THC relative to well-established antiepileptics on the frequency of cobalt-caused focal epileptic cortical potentials in conscious rats. Before any pharmacological experiments were undertaken, however, the stability of the frequency of focal potentials was evaluated by continuously recording during the 180-min test period in 7 vehicle control studies. The control study at the top of Fig. 1 illustrates the general experimental design: The first vehicle dose was administered 15 min after the beginning of the experiment; the second dose, 45 min after the first dose. Subsequently, the electrocorticograms were recorded for an additional 120 min. This time-effect relation seen in Fig. 1, is representative of the 6 other control studies. In short, potential frequency provides a relatively stable parameter for the pharmacological evaluation of anticonvulsant drugs.

The drug studies in Fig. 1 were identical in design to the controls, except that a drug preparation was substituted for the

FIG. 1. Influence of vehicle, Δ^9-THC, ethosuximide and trimethadione on the frequency of epileptic potentials at a cobalt-induced focus in the left parietal cortex. Each time-effect relation depicts the results from 1 animal; each point represents the mean frequency during a 5-min period. The arrows indicate the time of vehicle or drug administration.

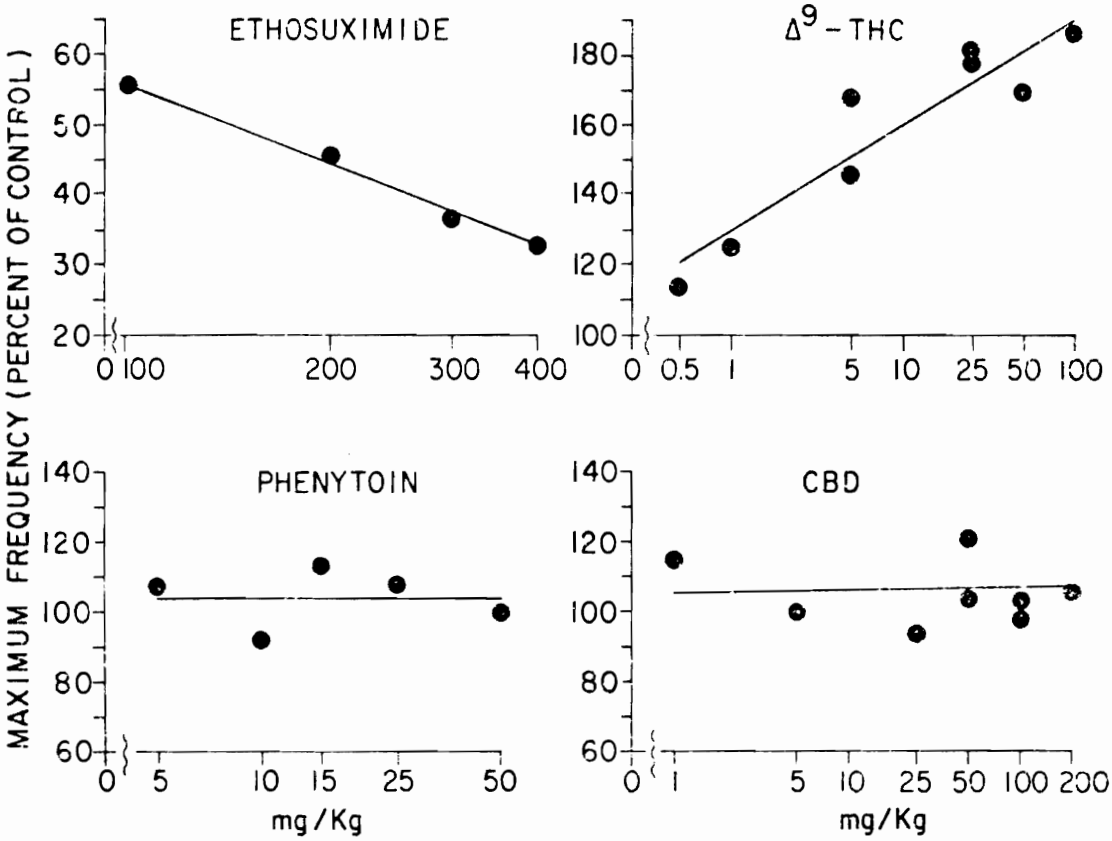

VEHICLE VEHICLE
VEHICLE Δ9-THC 25 mg/Kg
VEHICLE ETHOSUXIMIDE 200 mg/Kg
VEHICLE TRIMETHADIONE 400 mg/Kg
FREQUENCY (NUMBER / MINUTE)
CONTROL 0 30 60 90 120
MINUTES AFTER TREATMENT

second vehicle dose. The time-effect relations of the 3 drugs indicate that substantial alterations in frequency occurred following drug administration: Δ^9-THC markedly enhanced the frequency of focal potentials, whereas both ethosuximide and trimethadione reduced focal activity. Generally speaking, there were also some similarities among the three drugs: In the majority of experiments, the drug responses began within 15 min, persisted for at least 60 min, and concluded within 120 min. In a few experiments, the drug effects were still apparent at the end of the drug-test period. Time-effect relations, such as those shown in Fig. 1, were used to determine the maximum response produced by a drug dose; from the maximum response data, the dose-response relations illustrated in Fig. 2 were derived.

Dose-effect Relations

The dose-effect relations shown in Fig. 2 included doses that are known to exert anticonvulsant activity in various rat test systems: Δ^9-THC, 1-10 mg/kg (Corcoran et al., 1973; Consroe and Man, 1973; Karler et al., 1974d), CBD, 1 - 50 mg/kg (Izquierdo and Tannhauser, 1973; Karler and Turkanis, 1976a; Smiley et al., 1978), ethosuximide and trimethadione, 100-400 mg/kg (Goodman et al., 1949; Dow et al., 1973), and phenytoin, 5-10 mg/kg (Petty and Karler, 1965). As illustrated in Fig. 2, ethosuximide diminished the frequency of focal potentials in a dose-related manner; although the data is not

FIG. 2. Influence of ethosuximide, phenytoin, Δ^9-THC and CBD on the frequency of focal epileptic potentials at a cobalt-induced focus in the left parietal cortex. Each point represents the results from 1 animal and is the maximum frequency expressed as a percentage of predrug control. The lines were calculated by least squares regression.


ETHOSUXIMIDE
Δ9 – THC
PHENYTOIN
CBD
MAXIMUM FREQUENCY (PERCENT OF CONTROL)
mg/Kg
mg/Kg

shown, trimethadione in additional experiments yielded ethosuximide-like results. Phenytoin, in contrast, exerted no suppressant effect on cobalt-induced epileptic potentials (Fig. 2).

Δ^9-THC raised the frequency of focal potentials in a dose-related fashion, while CBD, like phenytoin, had no effect (Fig. 2). The data indicate that CBD, Δ^9-THC and phenytoin even in doses 5-10 times greater than their anticonvulsant dose 50 values, as determined by the maximal electroshock test, did not display an ethosuximide-like decrease in frequency. Thus, the mechanism of the anticonvulsant action of the cannabinoid does not appear to involve the abolition of focal epileptic potentials.

Focal Potential Frequency Increase and Bursts Caused by Δ^9-THC

In the present investigation, Δ^9-THC, unlike CBD and phenytoin, greatly enhanced the frequency of focal potentials (Figs. 1 and 2). Two different electrocorticographic phenomena at the focal recording site were noted after Δ^9-THC and both contributed to the overall increase in frequency: First, Δ^9-THC raised the frequency of cobalt-produced epileptic potentials at the focus (Fig. 3B1), but no epileptic potentials appeared at the other 3 recording sites (Fig. 3B2, 3B3, 3B4). Because this drug response was confined to the focus, the data suggest that Δ^9-THC selectively activated the epileptic focus.

Secondly, another type of epileptic-like electrical potential contributed to the Δ^9-THC-induced frequency increase. These potentials exhibited several features that distinguish them from the cobalt-induced spikes depicted in Fig. 3: First, they occurred in intermittent, discrete bursts of polyspikes (high voltage multiphasic potentials) (Fig. 4A-C); the modal duration of the bursts in 8 experiments ranged from 1.5-4.0 sec. Secondly, the bursts resembled after-discharges (ADs) produced by focal electrical stimulation of the cortex (Racine, 1975); and, compared with cobalt-induced spikes, the individual potentials within each burst exhibited a more symmetrical shape than that of the focal potentials (Figs. 3 and 4). Thirdly, the bursts did not occur prior to treatment but began to develop 45-60 min after drug and persisted for the remainder of the 120-min test period (Fig. 5). Fourthly, the bursts were generalized phenomena that were usually detectable from all 4 cortical recording sites. The bursts, however, did not appear to originate exclusively at the cobalt-induced focus because they were occasionally seen in one or more of the non-focal electrocorticograms, while being absent at the focus. Finally, the bursts made a relatively small contribution to the Δ^9-THC-caused increase in focal frequency: For example, over a range of 0.5-25 mg/kg of Δ^9-THC, the potentials associated with bursts amounted to less than 2% of the total number of epileptic-like potentials recorded; at 50 and 100 mg/kg, they were 8.2 and

FIG. 3. Influence of Δ^9-THC on the electrocorticogram of an epileptic rat. The recordings were obtained 20 min after either vehicle or drug. Each dot below the focal recordings (A1 and B1) indicates an epileptic potential.

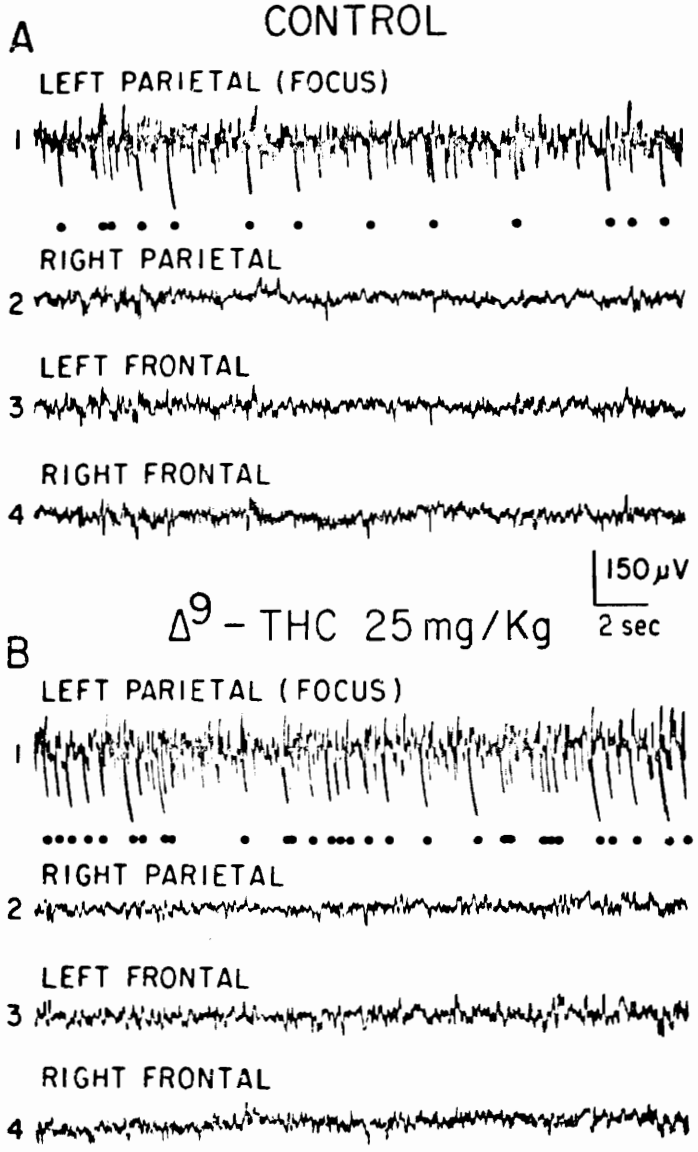

A
CONTROL
LEFT PARIETAL (FOCUS)
1
RIGHT PARIETAL
2
LEFT FRONTAL
3
RIGHT FRONTAL
4
150 μV
2 sec
Δ9 – THC 25 mg/Kg
B
LEFT PARIETAL (FOCUS)
1
RIGHT PARIETAL
2
LEFT FRONTAL
3
RIGHT FRONTAL
4

FIG. 4. AD-like bursts produced by Δ^9-THC, 11-OH-Δ^9-THC and PTZ. Responses A, B and C were obtained 81-90 min after Δ^9-THC; responses D, E, and F, 15-60 min after 11-OH-Δ^9-THC; responses G, H, and I, 16-20 min after PTZ.

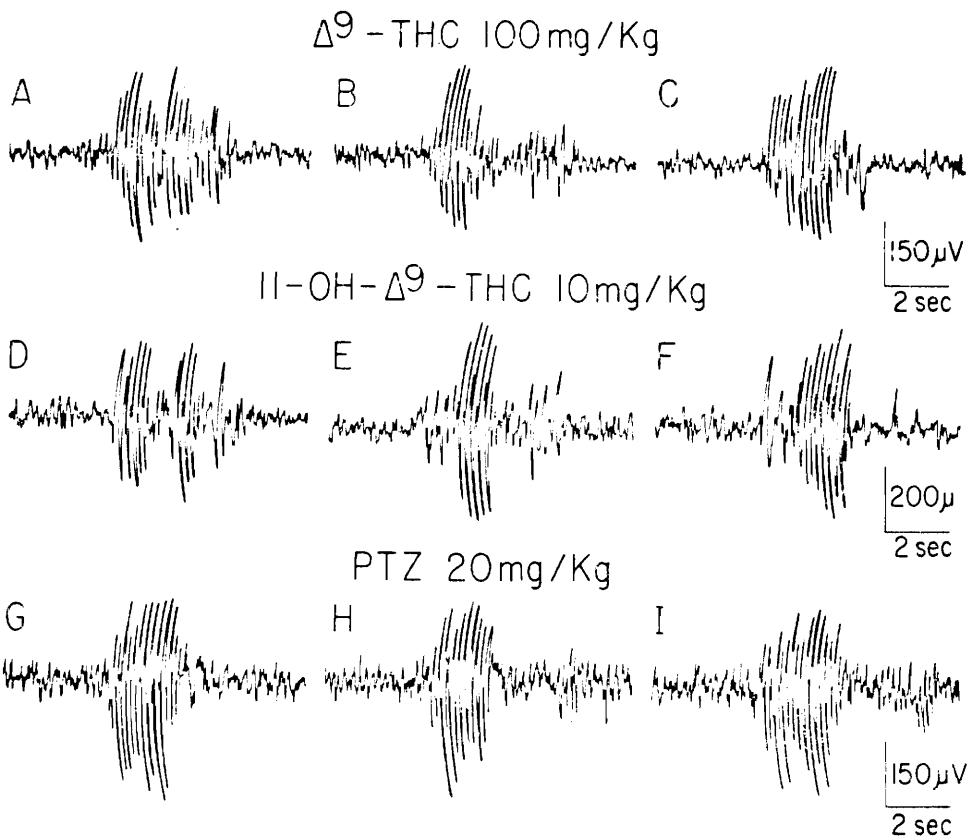
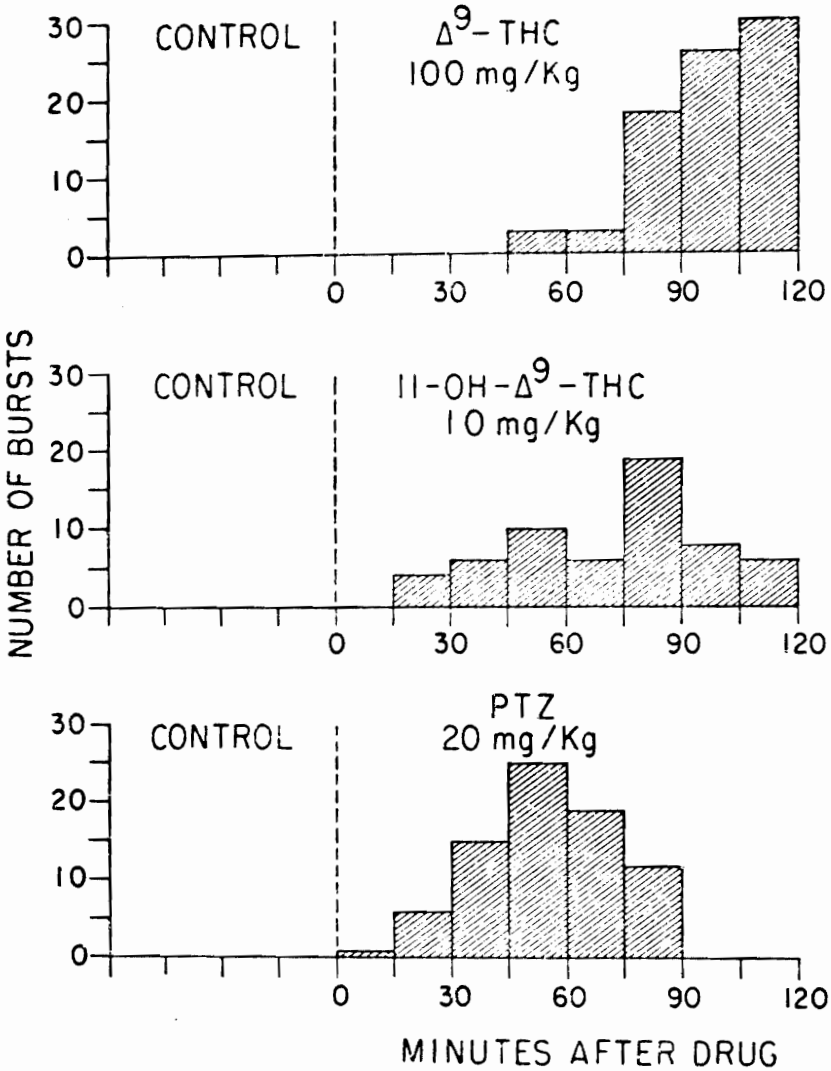

Δ9 - THC 100 mg/Kg
A
B
C
150 μV
2 sec
11-OH-Δ9 - THC 10 mg/Kg
D
E
F
200 μ
2 sec
PTZ 20 mg/Kg
G
H
I
150 μV
2 sec

FIG. 5. Time course of AD-like bursts produced by Δ^9-THC, 11-OH-Δ^9-THC and PTZ in epileptic rats. Each time-effect relation represents the results from 1 animal. Vehicle was given 15 min after the beginning of the control period; drug, at the beginning of 120-min test period; an additional dose of PTZ (20 mg/kg) was given at 45 min.


CONTROL
Δ9-THC
100 mg/Kg
CONTROL
11-OH-Δ9-THC
10 mg/Kg
CONTROL
PTZ
20 mg/Kg
NUMBER OF BURSTS
30
20
10
0
0
30
60
90
120
MINUTES AFTER DRUG

18.0%, respectively. The findings also suggest that moderate burst production requires relatively high doses of Δ^9-THC.

Other investigators have reported that marihuana extracts or Δ^9-THC induced polyspikes in normal animals (Pirch et al., 1972; see Truitt and Braude, 1975, for a review). Consequently, 10 experiments were carried out with control rats (no cobalt focus), and Δ^9-THC (1-100 mg/kg) caused polyspikes that were similar to those previously described by Pirch et al.(1972). The polyspikes were visually distinguishable from the cobalt-induced focal epileptic potentials and were always generalized and not focal in nature. Therefore, the data clearly demonstrate that Δ^9-THC did not induce focal potentials, such as those exhibited by a cobalt epileptic focus. In contrast, many of the polyspikes in normal animals resembled the Δ^9-THC-caused bursts in epileptic animals; however normal rats, unlike epileptic rats, often displayed so much variability in the shapes of these high voltage potentials that discrete bursts of polyspikes were frequently difficult to identify. Thus, the 11-OH-Δ^9-THC and PTZ experiments described below were carried out in epileptic animals so that both focal phenomena and generalized bursts could be reliably measured.

11-OH-Δ^9-THC Studies

A limited supply of 11-OH-Δ^9-THC, the major metabolite of Δ^9-THC, restricted the experiments to 3 animals and to a dosage

range of 10-20 mg/kg. In spite of such limitations, the studies provided a valuable comparison of the pharmacological properties of the metabolite and its parent compound. The 11-OH metabolite, unlike Δ^9-THC, did not produce a consistent effect on cobalt-caused focal epileptic potentials: an increase in frequency was found in one experiment, a decrease in another, and no change in the third. The 11-OH metabolite's dose may have been insufficient to cause an enhancement of the frequency of epileptic potentials. Raising the dose, however, was not possible because 20 mg/kg produced marked toxicity: For example, at this dose, the 11-OH-Δ^9-THC produced persistent circling behavior, which, under the conditions of the present investigation, did not occur with either Δ^9-THC or CBD.

In addition, the 11-OH compound (Fig. 4 D-F) produced generalized bursts, which were similar to those evoked by Δ^9-THC. A major difference between the 2 drugs was the 11-OH-metabolite's shorter onset time. Time-course data contrasting the differences in onset time between the 2 drugs are illustrated in Fig. 5: 11-OH-Δ^9-THC produced bursts in 15-30 min; Δ^9-THC, in 45-60 min.

PTZ Studies

PTZ was included in the present investigation as a reference drug, because Δ^9-THC and PTZ are known to exert similar central

excitatory responses in some electrophysiological test systems (Boyd et al., 1971a, b, 1974; Turkanis et al., 1977). PTZ experiments were carried out in a manner identical to that of the other drug studies, except that multiple doses of PTZ were usually administered during each experiment due to its relatively short duration of action. PTZ, unlike Δ^9-THC, seldom enhanced focal activity: In 5 multi-dose experiments, PTZ in subconvulsant doses (10-40 mg/kg) only augmented focal frequency once. In contrast, PTZ, like Δ^9-THC and 11-OH-Δ^9-THC, consistently produced generalized bursts, such as those seen in Fig. 4G-1. The time course of PTZ-caused bursts (Fig. 5) illustrates PTZ's rapid onset of action.

The data suggest that the bursts of polyspikes produced by Δ^9-THC or its 11-OH metabolite are manifestations of their central excitatory properties: First, these cannabinoids elicited generalized bursts similar to those produced by the central excitatory drug, PTZ. Secondly, the bursts caused by all 3 drugs resemble electrically evoked cortical ADs (Racine, 1975). Neither CBD nor phenytoin, even in high doses, induced any Δ^9-THC-like bursts; therefore, the major difference among the effects of CBD, phenytoin and Δ^9-THC in cobalt induced epileptic animals, as well as in other test systems (Karler et al., 1974d; Turkanis et al., 1974, 1977), is Δ^9-THC's CNS excitation.

Influence of the Cannabinoids on Motor Seizures

A comprehensive study of the drug influence on convulsions was not feasible, because only a small number of the epileptic rats displayed limb and jaw clonus. Although there are too few observations from ethosuximide, trimethadione and phenytoin experiments to warrant discussion, the vehicle and cannabinoid studies did provide valuable information: In 7 vehicle control experiments, 4 rats exhibited clonic activity throughout the 180-min test and vehicle treatment did not alter or induce convulsions in any of the control rats. In 8 Δ^9-THC studies, 1 animal during the predrug control period displayed clonus, which was exacerbated by 100 mg/kg of Δ^9-THC. Three other animals developed persistent clonic activity only after treatment with Δ^9-THC (25 or 50 mg/kg). In contrast, in 8 experiments, CBD in doses of 1-50 mg/kg abolished seizures in the 4 rats that exhibited clonus and CBD in doses as high as 200 mg/kg did not produce convulsions in any of the epileptic rats. The data suggest that CBD abolished seizures without affecting the focal abnormality; consequently, CBD may produce its anticonvulsant effect by depressing seizure spread within the CNS. In contrast, Δ^9-THC exacerbated both the electrical and motor manifestations of cobalt-caused epilepsy.

DISCUSSION

The results of the cannabinoid experiments on a cobalt-induced epileptic focus in the rat parietal cortex have provided information relative to the mechanism of the anticonvulsant action of CBD, as well as the potential toxicity of Δ^9-THC. Despite the well-documented anticonvulsant activity of Δ^9-THC (Karler and Turkanis, 1976a), the drug produced several CNS excitatory effects: It increased the frequency of focal epileptic potentials; it produced generalized bursts of epileptic-like polyspikes; and finally, it caused frank seizures. None of these excitatory effects were associated with CBD, even in very high doses.

Δ^9-THC's excitatory properties have been described previously; for example, Δ^9-THC exacerbated PTZ-caused minimal seizures (Karler et al., 1974d), caused withdrawal hyperexcitability in the 6-Hz and 60-Hz electroshock tests (Turkanis et al., 1978), prolonged electrically evoked hippocampal ADs (Feeney et al., 1973), enhanced electrically evoked cortical potentials (Boyd et al., 1971a, b, 1974), augmented photically evoked cortical ADs (Turkanis et al., 1977) and produced convulsions in epileptic beagles (Feeney et al., 1976),

in a special strain of rabbits (Martin and Consroe, 1976), as well as in normal rats (Stadnicki et al., 1974). The mechanism of the CNS excitation is not known; however, the present data demonstrate that Δ^9-THC directly activates an epileptic focus, which, in turn, suggests that marihuana may exacerbate certain focal epilepsies and would, therefore, be contraindicated in epileptics. There is one report in the literature linking the use of marihuana to the precipitation of grand mal seizures in a single patient (Keeler and Reifler, 1967), but in another patient, marihuana smoking enhanced the antiepileptic activity of phenobarbital and phenytoin (Consroe et al., 1975). The diversity of these very limited clinical observations may reflect the complexity of Δ^9-THC's known effects in animals: The drug not only produces numerous excitatory effects, but it also effectively blocks seizures in certain types of anti-seizure tests (Karler and Turkanis, 1976a, b). Whether the use of marihuana by epileptics will affect seizure control, remains to be determined; nevertheless, epileptic patients should be made aware of the potential hazards.

The investigation of the excitatory properties of Δ^9-THC was extended to its principal metabolite, 11-hydroxy-Δ^9-THC. The only consistent excitatory effect evoked by this metabolite was the production of the generalized epileptic-like bursts of polyspikes. The onset time of the effect (Fig. 5) was shorter in the case of the

metabolite than it was in the parent compound. The difference in onset time may indicate that the polyspike effect of Δ^9-THC is caused, at least in part, by its primary metabolite, which *in vivo* is very rapidly produced (Karler and Turkanis, 1976a). Conversely, the limited excitatory response to the 11-hydroxy derivative is evidence that the other excitatory effects of Δ^9-THC, an increase in focal epileptic potentials and frank seizures, are a consequence of Δ^9-THC itself. The recorded excitatory effects of the 11-hydroxy compound add to the accumulated evidence that some properties attributed to Δ^9-THC may be related to the production of active metabolites (Grunfeld and Edery, 1969; Brady and Carbone, 1973; Gill et al., 1973; Karler et al., 1974c; Turkanis and Karler, 1975, 1976; Karler and Turkanis, 1976a).

The use of the cobalt epilepsy model offers a test system that lends itself to a mechanistic study of anticonvulsant effects. The differential effects of ethosuximide, trimethadione and phenytoin on the frequency of focal potentials confirm the observations of Dow et al. (1973) and Scuvee-Moreau et al. (1977) and support the hypothesis that pharmacological investigation of cobalt-caused focal potentials may help to identify potentially useful drugs for the treatment of absence seizures. Previous studies of CBD have emphasized the similarity between its anticonvulsant properties and those of phenytoin (Karler and Turkanis, 1976a, b); however, there is some

evidence that CBD has ethosuximide-like properties (Smiley et al., 1978). In the cobalt model, CBD, unlike ethosuximide, did not seizures (Goodman and Lih, 1941; Karler et al., 1974d); it can prolong electrically evoked ADs (Gangloff and Monnier, 1957); and it can produce frank convulsions (Gruber et al., 1940). None of these excitatory effects was characteristic of CBD, even in very high doses (Karler et al., 1974d; Smiley et al., 1978.) There are only two reports of excitatory effects related to CBD, and both studies lacked proper controls (Perez-Reyes and Wingfield, 1974; Segal, 1974).

The excitatory effects of phenytoin are not unique for an antiepileptic because others, such as phenobarbital, ethosuximide and trimethadione, also exhibit excitatory effects (Dow et al., 1973; Littrow et al., 1970; Gangloff and Monnier, 1957). The CNS excitatory effects of these antiepileptics may contribute to their clinical toxicity, as evidenced by the ability of phenytoin to trigger absence seizures and ethosuximide to precipitate grand mal seizures (Woodbury and Fingl, 1975; Lorentz De Haas et al., 1964). If the hypothesis is correct that the excitatory effects of antiepileptics account for their exacerbation of certain types of seizures, then CBD, which appears to have little or no excitatory properties, may have a therapeutic advantage over some antiepileptics.

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