Potentiation of the epileptogenic effect of penicillin G by marihuana smoking[1,2]

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Marihuana smoking is known to produce many subtle neurological modifications in animal and man. We investigated the effects of subconvulsive doses of penicillin after acute or chronic marihuana smoking. Twenty-four mongrel dogs weighing from 15 to 25 kg received 4 mg morphine per kilogram, intramuscularly, and 750 000 IU sodium penicillin G per kilogram, intravenously. In acute experiments, the animals smoked eight cigarettes containing approximately 6 mg of Δ^9-tetrahydrocannabinol. In chronic experiments, they smoked four cigarettes per day for 10 weeks before being studied. Ten animals (five controls and five acute smokers) were observed visually while the electrocorticogram (ECoG) was recorded in the 14 others (five controls, five acute, four chronic). This last group received 20–30 mg succinylcholine chloride as muscle relaxant. Penicillin had no effect either on the behaviour or on the ECoG in 9 of the 10 controls. On the other hand, 9 out of the 10 acute smokers showed modifications (coarse tremors of the limbs and epileptiform waves). Two of the four chronic smokers had typical epileptiform episodes. The results suggest that marihuana smoking produces a blood–brain barrier permeability change towards sodium penicillin G. Another explanation could be that *Cannabis* modifies the excitability threshold of the brain.

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Diverses études démontrent que l'usage aigu ou chronique de marihuana peut entraîner des modifications neurologiques chez l'animal et l'homme. Dans cette étude, nous avons déterminé les effets de doses subconvulsives de pénicilline G chez des animaux ayant fumé de la marihuana. Vingt-quatre chiens pesant de 15 à 25 kg reçurent morphine (4 mg/kg, im) et pénicilline G sodique (750 000 IU/kg, iv). En expérimentation aiguë, les chiens fumèrent huit cigarettes contenant chacune 6 mg de Δ^9-tetrahydrocannabinol alors que les quatre sujets chroniques fumèrent quatre cigarettes par jour pendant 10 semaines avant de participer à l'expérience. Dix chiens (cinq témoins, cinq aigus) furent observés visuellement alors que l'electrocorticogram (ECoG) fut étudié chez les 14 autres (cinq témoins, cinq aigus, quatre chroniques). Ces derniers reçurent 20–30 mg de chlorure de succinylcholine comme relaxant musculaire. La pénicilline ne perturba ni le comportement ni l'ECoG de 9 des 10 témoins. Par contre, 9 des 10 fumeurs aigus montrèrent des modifications (soubresaults et ondes épileptiforms). Chez le quatre fumeurs chroniques, deux sujets montrèrent des crises épileptiformes typiques. Ces résultats suggèrent que l'usage de marihuana produit une modification de la perméabilité de la barrière hémo–encéphalique à la pénicilline G. Une autre explication pourrait être que le *Cannabis* modifie l'excitabilité neuronale.

Introduction

A number of investigations have been carried out during the past few years to determine the behavioural and neurological effects of marihuana. From animal studies, it became apparent that no gross pathological changes could be observed except when very high doses of Δ^9-THC were administered. On the other hand, many studies both in rats and in man showed that subtle neurological changes may be observed after marihuana use. For

ABBREVIATIONS: Δ^9-THC, Δ^9-tetrahydrocannabinol; EEG, electroencephalogram; ECoG, electrocorticogram; DMPH, dimethylheptyl pyran; GM, grand mal; CNS, central nervous system; BBB, blood–brain barrier.

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[2]Some of the results from this study were presented at the 19th Annual Meeting of the Canadian Federation of Biological Societies, Halifax, 1976.

instance, disruption of complex memory patterns and alteration of visual discrimination were reported in monkeys (Scheckel *et al.* 1968) and pigeons (Siegel 1969). In man, Rodin *et al.* (1970) allowed healthy medical students to smoke two to three National Institute of Mental Health (NIMH) marihuana (1.312% THC) cigarettes. They did not notice significant neurological alterations in these subjects. Mental status examination, however, revealed minor disturbances such as a slight decrease in intellectual efficiency, excessive jocularity, a slight loosening of the capacity of association, and short-term memory loss. In further pharmacological studies conducted with 16 student volunteers, Domino (1971) reported that four subjects had visual and auditory hallucinations and one had a very severe panic reaction.

Changes in the EEG and the ECoG were reported in animals after the administration of some natural and synthetic THC derivatives. In rats, *Cannabis sativa* extract induced bursts of polyspikes on the ECoG (Masur and Kazan 1970). These high-voltage bursts had frequencies ranging from 8 to 12 Hz and amplitudes up to 600 μV. These were observed both in the awake animal and at the end of the sleep period. In cats with indwelling electrodes, Hockman *et al.* (1971) showed that intraperitoneal administration of THC (0.5 and 1.0 mg/kg) produced high-voltage slow waves on the EEG of awake and moving animals. The effect usually began between 5 and 15 min after the injection and reached a peak between 30 and 45 min. The increase in synchrony of the EEG was also observed with the dose of 4 mg/kg. However, the amount of high-voltage activity was less with this dose in comparison with the smaller doses. Similar results were also reported by Longo (1974). Lipparini *et al.* (1969) observed that the administration of 0.5–1.0 mg of Δ^9-THC per kilogram brought about a generalized reduction in voltage of EEG waves and some spike-and-wave complexes. Finally, in EEG recordings from monkeys, Domino *et al.* (1971) observed that the startle response to noise was exaggerated after DMHP administration. Furthermore, some convulsive movements could also be detected.

This manuscript describes the potentiation of the neurotoxicity of penicillin G by acute and chronic marihuana smoking in dogs. It provides a useful animal model to study the effects of *Cannabis* intoxication on brain physiology.

Methods

Twenty-four mongrel dogs weighing between 10 and 25 kg were used in these experiments. A tracheotomy was performed on all animals 4 to 7 days prior to the beginning of the experimentation. In chronic animals, a silastic tracheotomy tube was implanted for the duration of the intoxication period. Mongrel dogs were utilized because this species is more suitable for tracheostomizing and administering marihuana by cigarettes. Furthermore, the techniques and the technicians required for this type of experiment were readily available to us as some of our colleagues from le Centre de Recherche had a long experience in this area (Huy *et al.* 1975; Huy and Roy 1976; Roy *et al.* 1976).

TABLE 1. Summary of the experimental conditions

Experimental conditions	Control		Marihuana	
	Type I	Type II	Acute	Chronic
Marihuana	0	+	+	+
Morphine	+	+	+	+
Succinylcholine	+[a]	+[a]	+[a]	+[a]
Saline				
Before injection of penicillin	+	+	+	+
Instead of the injection of penicillin	0	+	0	0
Penicillin	+	0	+	+
n < Gross behaviour	0	5	5	0
n < ECoG	2	3	5	4

[a]Omitted in the case of the animals utilized in gross behaviour experiments.
NOTE: 0, indicates that the drug was not administered; +, indicates that the drug was administered.

Marihuana was administered by inhalation using the method described by Cahan and Kirman (1968). The cigarettes each contained 6 mg of Δ^9-THC. The chronic animals smoked four cigarettes daily for 10 weeks. On the day of the experiment, both the acute and chronic dogs smoked eight marihuana cigarettes prior to the beginning of experimentation. The dose of marihuana administered at this moment was relatively small. Indeed, each dog received a total of 48 mg THC for they smoked eight cigarettes, each containing 6 mg THC. The mode of administration of the drug, i.e. inhalation, reduced further the actual dosage administered. Indeed, Fehr and Kalant (1972) as well as Truitt (1971) showed that 50% or less of the inhaled THC could be found in the blood stream. Then, the dose of THC that was given to our animals varied between 1–2.5 mg/kg for the animals weighing between 10 and 25 kg.

The neurological effect of penicillin was studied on gross behaviour as well as on ECoG recordings. The animals were divided at random into four groups. The experimental conditions utilized in each group are presented in Table 1. For ethical reasons, it was decided that the animals required some analgesia. Thus, all animals received 4 mg of morphine sulfate per kilogram, intramuscularly (Stobel and Wollman 1969). In the animals utilized in gross behaviour experiments, the administration of succinylcholine was omitted. A dose of 750 000 IU of sodium penicillin G per kilogram was injected into the femoral vein. This dosage was divided into two equal fractions administered at 20-min intervals. As a control measure, a 2-ml saline injection was always administered before penicillin. The effect of the large dose of the antibiotic was continuously monitored for 4–6 h after injection of the drug to animal.

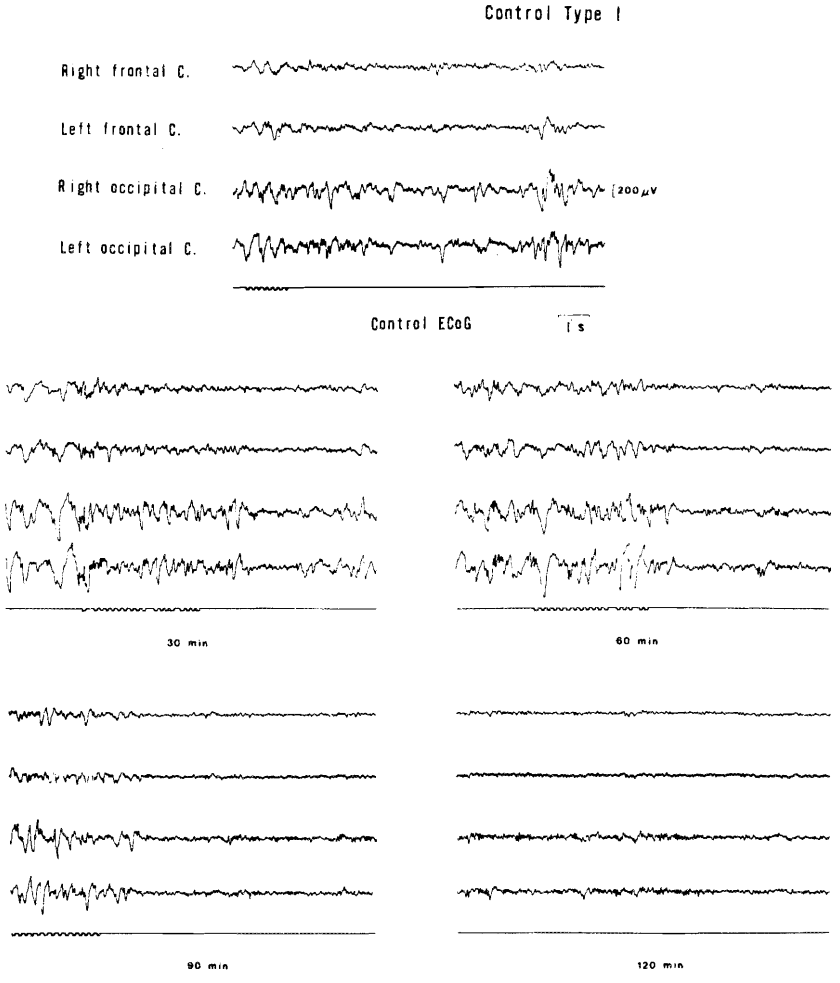

FIG. 1. Effect of penicillin G (750 000 IU/kg, iv) on the ECoG of control group type I dog. In animals who did not smoke marihuana, the large dose of antibiotic did not produce any convulsive manifestation.

In the remaining animals, the effects of penicillin on ECoG recordings were obtained using four brass screw electrodes inserted into the skull. The indifferent electrode was placed in the midline of the frontal bone for monopolar recording. All animals utilized in this section received 20–30 mg of succinylcholine chloride as muscular relaxant. Respiration was supported mechanically. In all animals, a volume of saline (2 ml) was always injected during the control period. In some animals (control group type II) another volume of saline was given intravenously to replace the injection of penicillin. In all these experiments, the dose of the antibiotic and its mode of administration were similar to what were used in gross behaviour experiments.

The drugs used in these experiments and their sources were as follows: marihuana, the Non-Medical Use of Drug Directorate of the Medical Research Council of Canada, Ottawa; penicillin, Ayerst laboratories, Montreal; succinylcholine chloride, Burroughs Wellcome Ltd., Montreal, P.Q.; morphine sulfate, Department of Pharmacology, Université Laval, Quebec.

Results

A. Gross Behavioural Effect of Penicillin G

During the 3-h observation period, four of the five control animals appeared normal and tranquil. The fifth animal in this group showed occasional muscular jerks of the limbs. The autopsy did not reveal any gross cerebral pathology. Conversely, muscular jerks were noted in four of five acute marihuana smokers while clonic movements were observed in the fifth animal of this group. All animals survived the experiment and appeared normal 24 h later.

B. ECoG Effect of Penicillin G

1. Control group

ECoG tracings typical of the control group type I

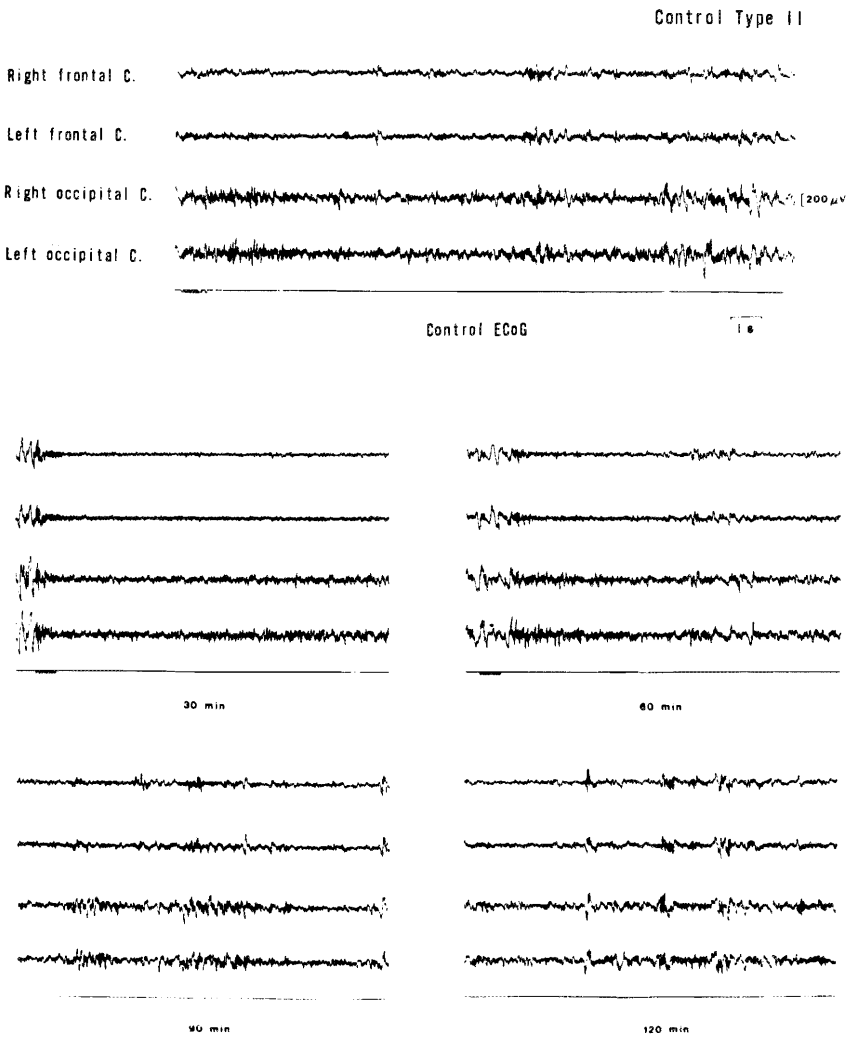

FIG. 2. Effects of smoking eight marihuana cigarettes on the ECoG of control group type II dogs. In this series of experiments, equal volumes of saline were injected instead of penicillin.

are illustrated in Fig. 1. Immediately before the administration of the antibiotic, low-frequency (6–8 cps) high-amplitude waves typical of a sedated animal were recorded. External stimulation produced by tapping the animal on its back is indicated in the figure by depressions of the lower line. It produced an arousal reaction lasting approximately 10 s. The tracings obtained 30, 60, 90, and 120 min after the second penicillin injection were basically similar to the control tracings. In the lower right tracing, the waves had a low amplitude indicating that the sedation due to morphine had disappeared.

Figure 2 illustrates the effects of smoking eight marihuana cigarettes on the ECoG. In these experiments the injections of penicillin were replaced by equivalent volumes of saline (control group type II). During the control period, slow waves characteristic of drowsiness were observed. The arousal reaction was present. Sixty, 90, and 120 min after the saline injections, bursts of high-amplitude and low-frequency waves were recorded in the four cortical leads utilized.

2. Acute Marihuana Smokers

Figure 3 illustrates the effects of penicillin in dogs that smoked eight marihuana cigarettes. The tracing recorded before the administration of the antibiotic was characteristic of sleep. External stimulation produced a transient arousal reaction. Thirty minutes after penicillin G, the ECoG waves recorded did not differ significantly from those ob-

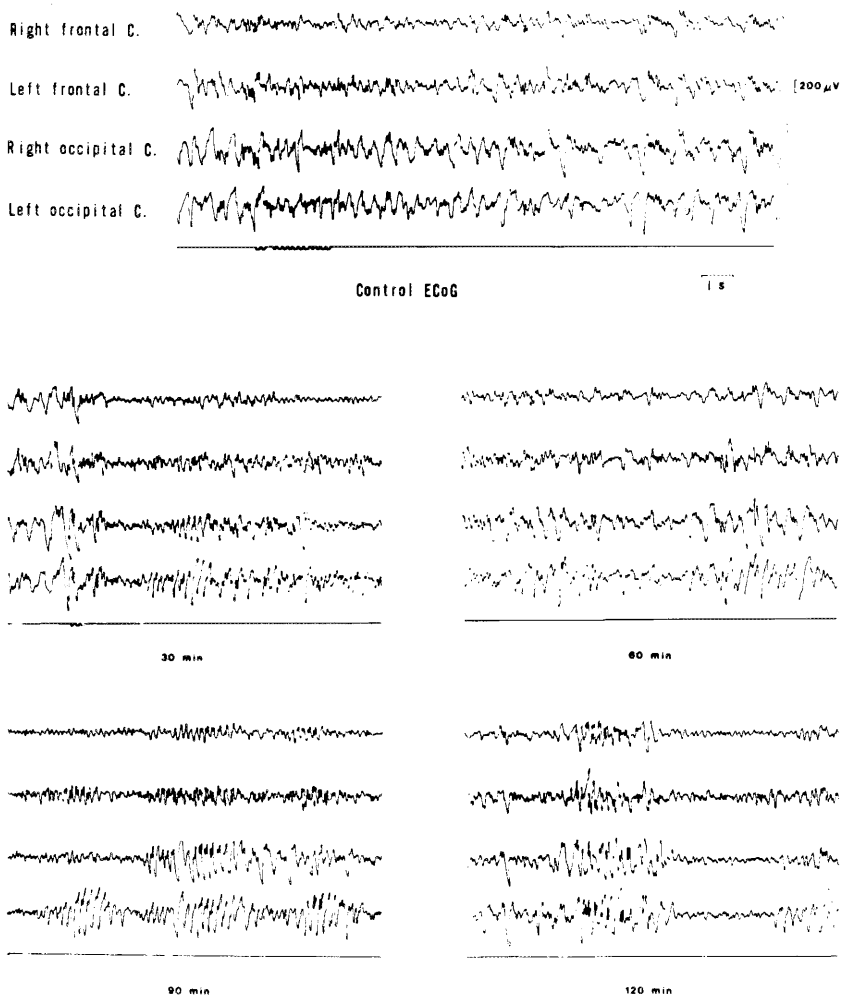

FIG. 3. Effects of penicillin G (750 000 IU/kg, iv) on the ECoG of dogs that had smoked eight marihuana cigarettes. Note the spike-and-wave pattern which appeared spontaneously at 90 min.

tained during the control period. External stimuli, however, produced epileptiform waves instead of an arousal reaction. These abnormal waves which lasted 3 s had an 8- to 10-cps frequency and an amplitude of 100–350 μV. They were localized in the occipital cortex. Ninety and 120 minutes after administration of the antibiotic, the epileptiform waves appeared spontaneously. These formed spindles lasting 3–6 s. It should also be noted that immediately prior to or after the epileptiform waves, the tracings were desynchronized. This effect was observed both in acute and in chronic marihuana smokers.

3. Chronic Marihuana Smokers

Figures 4*a*, 4*b*, and 4*c* present the ECoG tracings obtained in three of the four dogs that had smoked marihuana for 10 weeks. The first animal studied weighed 25 kg. As shown in Fig. 4*a*, the ECoG recorded during the control period was that usually observed in a drowsy animal. External stimulation produced a characteristic arousal reaction. Thirty minutes after the injection of penicillin epileptiform waves appeared spontaneously in the right frontal and in both occipital cortices. The spike-and-wave complexes had a 6- to 8-cps frequency, an amplitude of 100–300 μV, and lasted 3–5 s. These abnormal waves were present throughout the experiment. They could also be induced by an external stimulus such as a loud noise. This animal did not show any GM seizures. The second animal studied weighed 21.4 kg and gave somewhat similar tracings.

The first GM seizure was observed in a 16.8-kg dog. It is presented in Fig. 4*b*. The control ECoG was that of a sleeping animal and the short arousal

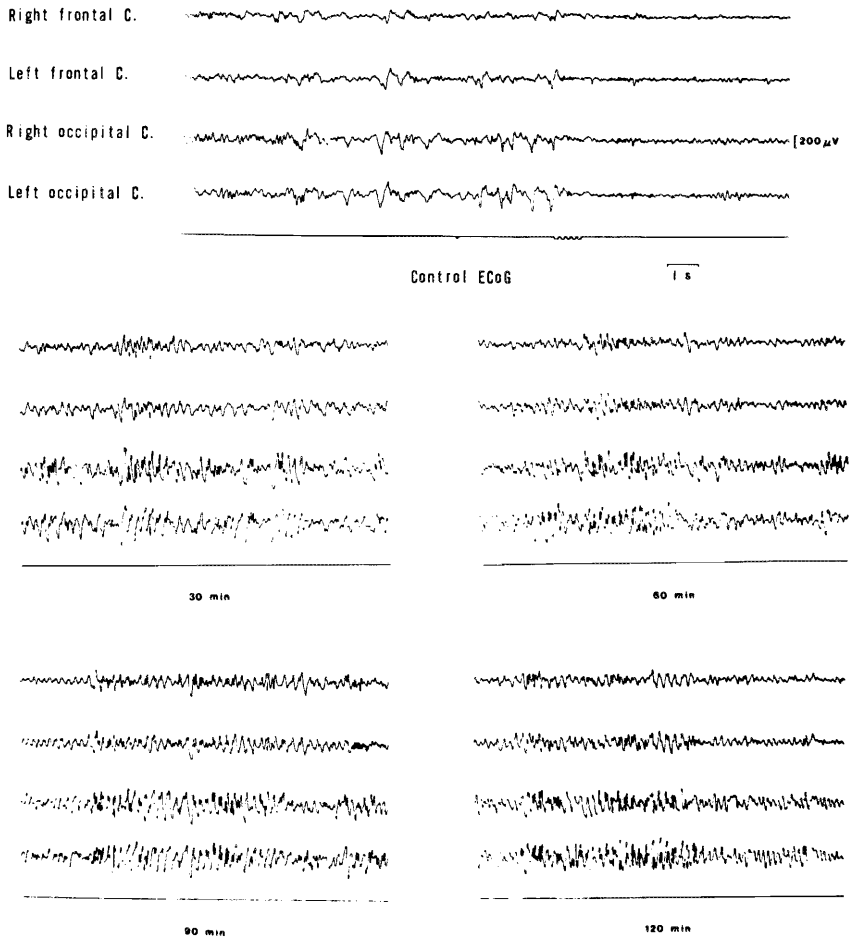

FIG. 4*a*. Effects of penicillin G on the ECoG of a 25-kg dog which had smoked four marihuana cigarettes daily for 10 weeks. High amplitude waves as well as spike-and-wave patterns appeared spontaneously at 30 min and lasted throughout the experiment.

reaction was typical. The first spike and wave patterns appeared 15 min after the second antibiotic injection. An external stimulus produced paroxysmal discharges in the right frontal and left occipital cortices. Sixty-nine minutes after penicillin as well as immediately before the GM seizure, spontaneous paroxysmal discharges occurred in all cortical leads. A typical GM seizure was observed 90 min after the antibiotic injection. The episode was characterized by a series of spike-and-wave complexes which were followed by hypersynchronized polyspikes and an electrical silence lasting 15 s. The total duration of this seizure was 112 s. This GM episode was the only one observed in this animal. Paroxysmal discharges were present in all cortical leads during the rest of the experiment, however.

The smallest animal of this group weighed 12 kg. It suffered 13 GM seizures during the $2\frac{1}{2}$ h of the observation period. As can be noticed in Fig. 4*c*, the ECoG recorded during the control period was similar to those obtained in other marihuana smokers. Twenty minutes after the administration of penicillin a series of polyspikes appeared spontaneously in the left frontal cortex. These waves had a frequency of 6–8 cps, a 4- to 600-μV amplitude, and lasted 1 s. The first convulsion appeared 10 min later. The wave patterns preceding and following the GM episode were similar to those described for Fig. 4*b*. In this animal, there was a GM seizure every 6–7 min for the duration of the experiment. These seizures lasted between 90 and 150 s while the duration of the neuronal silences following the seizures varied between 12 and 45 s.

Discussion

This study demonstrates that acute and chronic

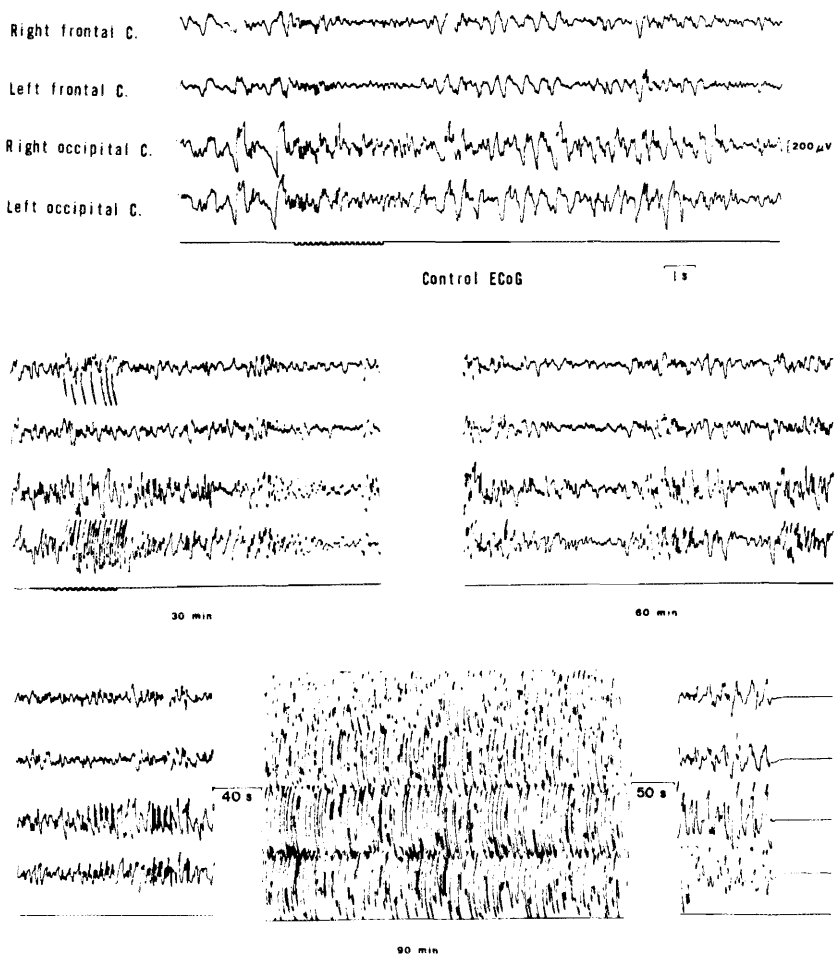

FIG. 4*b*. Effects of penicillin G on the ECoG of a 16.8-kg dog which had smoked four marihuana cigarettes daily for 10 weeks. A GM seizure was observable 90 min after the administration of the antibiotic.

marihuana smoking potentiates the neurotoxicity of penicillin in dogs in the presence of morphine. In acute smokers, subconvulsive doses of the antibiotic produced muscular jerks and some clonic movements. Stimulation-induced as well as spontaneous spike-and-wave patterns were observed in ECoG tracings. In chronic smokers, typical GM seizures were found. Figure 5 summarizes the data.

The dose of marihuana administered in our experiments did not produce by itself any major effect on gross behaviour or on ECoG. This observation was not surprising considering the small amount of marihuana (1–2.5 mg/kg) administered. The intoxication regimen utilized in these experiments must be considered as very conservative, particularly if one considers the levels of intoxication (0.1–3 mg/kg) reported for humans (World Health Organization 1971). On the other hand, the dose of penicillin may appear quite large. It must be remembered, however, that such a dose did not produce any convulsions in control animals (see Fig. 1). This finding is in agreement with the work of Dobell *et al.* (1966) who showed that intravenous administration of as much as 2 million IU of penicillin G per kilogram did not induce convulsions in normal dogs.

The observation that a single exposure to marihuana was sufficient to potentiate the neurotoxicity of penicillin was surprising. Indeed, the low doses of marihuana used, the short time of exposure, and the fact that the drug is highly bound to plasma proteins (Widman *et al.* 1971; Fehr and Kalant 1972; Paton *et al.* 1975) led us to expect very few acute toxic effects. Although the signs of neurotoxicity were rather mild in acute animals, they are alarming. They must be considered as precursors

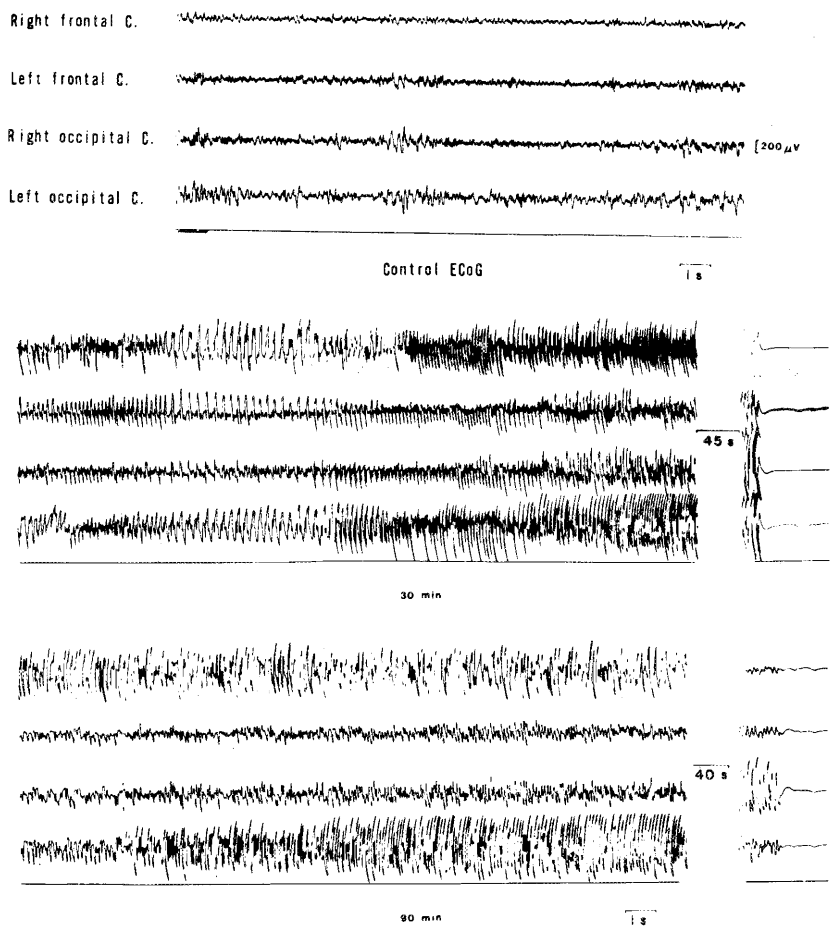

FIG. 4c. Effects of penicillin G on the ECoG of a 12-kg dog which had smoked four marihuana cigarettes daily for 10 weeks. A GM seizure was recorded every 6–7 min during the 2½ h of the observation period.

	Controls	Acute smokers	Chronic smokers	
	Results	Results	Weight/kg	Results
VISUAL	–	×		
	–	×		
	–	××		
	–	×		
	×	×		
ECoG	–	+	(25)	++
	–	++	(21.4)	+++
	–	+	(16.8)	++++
	–	++	12	+++++
	–	+		

–: no convulsions
×: muscular contractions
+: occasional spikes
++: series of spikes
+++: spike and wave
++++: grand mal (1)
+++++: status epilepticus

FIG. 5. Summary of the results obtained in the experiments.

of the dramatic effects obtained after chronic use of the drug.

It can be rightly argued that the use of morphine in our experimental conditions complicates the interpretation of the results. In the early phase of the experimentation, the authors discussed many times the possibility that the neurotoxicity of penicillin could be potentiated by morphine. However, on the recommendation of the local animal ethics committee (LAEC), it was decided that some analgesic drug must be administered to the animals to reduce the pain produced by the implantation of the ECoG electrodes in the skull. According to Strobel and Wollman (1969), the dose of morphine sulfate required to produce a good analgesia in dogs varied between 2 and 5 mg/kg. Therefore, the dose of 4 mg/kg was chosen to fulfill the desire of the LAEC. To check the possibility of an interaction between morphine and penicillin, the effect of the large dose of the antibiotic was studied in ani-

mals which received morphine and penicillin but no marihuana (see Fig. 1, control type I dogs). The results show that administration of the narcotic agonist did not potentiate the neurotoxicity of penicillin. We were also worried about a possible interaction between morphine and marihuana in our animals. Consequently, we ran another series of experiments where the two centrally acting drugs were administered to dogs receiving an injection of saline instead of penicillin. These are the control type II dogs. The results presented in Fig. 2 did not reveal any sign of such an interaction. Although the possibility of an interaction between morphine and penicillin cannot be ruled out in marihuana-smoking dogs, we strongly feel that such an interaction is improbable in this case.

Two hypotheses may be put forward to explain the data. The first is that marihuana smoking may lower the epileptic threshold of the brain. Thus, the small concentration of penicillin which may be found in the CNS after parenteral administration (Auvergnat 1972, 1974) would be sufficient to trigger the seizures. In this case, pharmacokinetic studies would not reveal any modification in the kinetics and content of the antibiotic in cerebral tissue or in the cerebrospinal fluid. This hypothesis is worth pursuing for Martin and Consroe (1976) recently showed that low doses of cannabinoid (0.5 mg THC/kg) may induce behavioural convulsions in rabbits. However, it should always be kept in mind that many reports in the literature showed previously that THC derivatives have an anticonvulsant property (Chester and Jackson 1974; McCaughan *et al.* 1974; Turkanis *et al.* 1974; Wada *et al.* 1974). This well-known pharmacological effect of THC therefore weakens but does not rule out our first working hypothesis.

The second hypothesis is that marihuana smoking increases the BBB permeability to penicillin. Consequently, the antibiotic concentration in the brain of treated animals would be expected to be much greater in the smoking animals than in controls. Presumably the level obtained in marihuana smokers would then be sufficient to induce convulsions.

Although both mechanisms may be involved in the production of the effects obtained in this study, our data suggest that BBB alteration may be the most important in this case. Indeed, the dose of penicillin utilized is known to induce convulsions in dogs that suffered serious BBB damage (Wyant and Dobell 1967). Furthermore, the period of time elapsed between the injection of the antibiotic and the appearance of the epileptic manifestations is shorter in chronic dog smokers than in acute smokers. Indeed, in acute animals spontaneous epileptic waves first appeared 90 min after the injection of penicillin (see Fig. 3) while in chronic dogs they were apparent at 30 min (see Figs. 4*a*, 4*b*, and 4*c*). These data suggest that convulsive brain concentration of the antibiotic is achieved more rapidly in chronic than in acute animals. A possible explanation for this observation is that *Cannabis* smoking alters the BBB integrity in such a way that the entry of drugs into the CNS is increased.

Our second hypothesis is also strengthened by the work of Lawrence and Gill (1975) who showed that even low concentrations of Δ^9-THC may render the lipid layer of cell membranes more fluid. Finally, it is also in agreement with the work of Agnew *et al.* (1976) who suggested that *Cannabis* (10–20 mg/kg) may alter or damage the active transport system of the choroid plexus. This last observation tends to support our hypothesis of subtle selectivity or permeability changes in the BBB leading later to more serious neurological symptoms.

Further research is needed to characterize the results described in this manuscript. Other laboratory animals with a more uniform genetic character than the mongrel dogs should be utilized. The use of pure Δ^9-THC, a complete dose–effect curve, and the use of topical penicillin would be very helpful to determine the mechanism responsible for the effect observed in our research. However, our observations should lead clinicians to exercise the greatest caution when administering high doses of penicillin to pot smokers. Hopefully, the interaction of penicillin with marihuana will soon be better documented.

Acknowledgments

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