STUDIES OF THE ANTICONVULSANT SPECTRUM OF Δ9-TETRAHYDROCANNABINOL IN RATS

by

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STATEMENT BY THE AUTHOR

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ABSTRACT

Delta 9-tetrahydrocannabinol (Δ9-THC), given orally was studied for anticonvulsant activity against electroshock seizures, and for anticonvulsant activity as well as protection from lethality against subcutaneous pentylene-tetrazol (PTZ), picrotoxin, and strychnine, and intraperitoneal lidocaine in rats. Δ9-THC in a dose-related fashion elevates the threshold for maximal electroshock seizures. A dose of 30 mg/kg of Δ9-THC provides anticonvulsant activity against maximal PTZ seizures while the same dose does not protect against maximal seizures induced by strychnine or minimal seizures induced by electroshock, PTZ, lidocaine or picrotoxin. Further, Δ9-THC at 30 mg/kg does not protect against lethality induced by any of the chemical convulsants used. These data indicate that Δ9-THC has a rather narrow anticonvulsant spectrum of activity involving only maximal electroshock and PTZ seizures. In these respects, Δ9-THC resembles phenytoin.
CHAPTER 1

INTRODUCTION

Within the last few years, research interest has been stimulated in the anticonvulsant properties of Delta 9-tetrahydrocannabinol (Δ9-THC) and various other cannabinoids found in marihuana (e.g., Δ8-THC, cannabidiol) as well as a metabolite of Δ9-THC, 11-hydroxy-Δ9-THC. In general, the anticonvulsant studies of Δ9-THC and these other cannabinoids have been conducted using seizures produced by sound, electrical, or chemical methods.

In sound induced seizures, i.e., audiogenic seizures, protection has been shown for Δ8-THC (Consroe and Man, 1973), Δ9-THC (Boggan, Steele and Freedman, 1973; Consroe and Man, 1973), cannabidiol and marihuana extract (Carlini, Leite, Tannhauser, and Berardi, 1973).

Furthermore studies using electrically induced seizures have shown protection by Δ8-THC and Δ9-THC (Consroe and Man, 1973; McCaughran, Corcoran and Wada, 1974; Sofia, Solomon and Barry, 1971), cannabidiol (Karler, Cely and Turkanis, 1973; Izquierdo and Tannhauser, 1973) and cannabinol (Karler et al., 1973) against maximal electroshock seizures (MES). In addition, Δ9-THC (Karler, Cely and Turkanis 1974a) and cannabidiol (Turkanis, Cely, Olsen, and Karler, 1974a)
have been shown to raise the threshold for minimal seizures induced by 6-Hz electrical stimulation but not to alter the threshold for 60-Hz induced minimal seizures. Cannabidiol (Carlini et al., 1973; Turkanis et al., 1974), Δ8-THC and Δ9-THC (Consroe and Man, 1973) demonstrate anti-convulsant activity against maximal seizures induced by pentylenetetrazol (PTZ). In contrast the effect of Δ9-THC on minimal PTZ seizures has produced equivocal results (Consroe and Man, 1973; McCaughran et al., 1974; Sofia et al., 1971).

In other studies Δ8-THC, Δ9-THC, cannabidiol, and cannabinol have been shown to raise the threshold for seizure discharges registered from the hippocampus following electrical stimulation of various brain sites (Izquierdo and Orsingher, 1973). Also Δ9-THC has been shown to block "kindled" seizures induced by amygdaloid stimulation (Corcoran, McCaughran and Wada, 1973). However in photomyoclonic seizures in baboons Δ9-THC has elicited equivocal results (Killam and Killam, 1972; Meldrum, Fariello, Puil Derovaux and Naquet, 1974).

It is apparent from these studies that some cannabinoid compounds have anticonvulsant properties in a variety of seizure paradigms. There is however a lack of information concerning the effects of the cannabinoids on seizures or lethality induced by chemical convulsants other than PTZ. Such studies are important to provide additional
information on the spectrum of anticonvulsant activity, the effect on lethality induced by convulsant drugs, and possible mechanisms of action for the cannabinoids.

The present study was designed to obtain information on the anticonvulsant activity of one cannabinoid, Δ9-THC, against four chemical convulsants: strychnine, picrotoxin, lidocaine, and PTZ, and to further quantitate and compare the anticonvulsant properties of Δ9-THC against electroshock seizure models. Further studies were done to test the effects of Δ9-THC on lethality induced by the convulsant drugs.

Δ9-THC was chosen to study since it has been more extensively characterized than the other cannabinoids as an anticonvulsant and thus would provide a broader basis for comparison of its effects across seizure models.
CHAPTER 2

GENERAL PROCEDURES

Experimental Animals

Male Sprague-Dawley rats,\(^1\) weighing 250-350 grams were used. Animals were allowed free access to food and water. Rats were housed, eight per cage, in a room maintained at a constant temperature of 25±2°C and under controlled lighting, i.e., an equal cycle of light (0600-1800 hours) and darkness (1800-0600 hours).

Animals were arranged in groups of ten for each experimental procedure. Each group of animals was selected by drawing animals at random from cages of naive animals.

Drugs

\(\Delta 9\)-THC was prepared for oral (p.o.) administration in the following manner: Stock solutions of \(\Delta 9\)-THC dissolved in ethanol were stored in vials at -21°C and protected from light. Immediately prior to use, the solution of \(\Delta 9\)-THC was transferred to a metal homogenization cannister which had previously been weighed. The vehicular ethanol was then removed using a vacuum apparatus. To insure complete removal of ethanol, the cannister was maintained under the

1. Holtzman Co., Madison, Wisconsin
vacuum apparatus until the weight of the Δ9-THC in the cannister was equal to the weight of Δ9-THC contained in the stock vial. Polysorbate (Tween) 80 and sesame oil were then added to the cannister and this mixture was then homogenized for 1 minute on a Servall-omni-mixer homogenizer at 16,000 rpm. Normal saline (0.9% NaCl was added in approximately 5 equal portions following the first homogenization and following each addition of saline, the mixture was homogenized for 30 seconds. Finally, normal saline was added to make the appropriate volume and the final mixture was homogenized for 2 minutes. The final emulsion consisted of Δ9-THC 5 mg/ml in a vehicle of 10% sesame oil, 1% Tween 80, and 89% normal saline. To insure even distribution of Δ9-THC in the emulsion, the mixture was shaken vigorously on a vortex shaker immediately preceding each administration.

The control animals were treated with Δ9-THC vehicle which consisted of 10% sesame oil, 1% Tween 80, and 89% normal saline.

Δ9-THC was administered orally 1 1/2 hours before electroshock administration or administration of a convulsant drug. Preliminary studies showed this to be the time of peak effect for maximal electroshock seizure protection following oral Δ9-THC. In the chemical convulsant experiments the animals received 30 mg/kg of Δ9-THC. This dose was determined in a preliminary study to be the 80%
protective dose (ED80) against MES, and was thus chosen as a standard to compare the effects of Δ9-THC in the electroshock model against its effects in chemical seizure models. PTZ, picrotoxin, strychnine sulfate and lidocaine hydrochloride were dissolved in normal saline. Doses of PTZ and picrotoxin were calculated as the free base while doses of strychnine and lidocaine were calculated as the salt. PTZ, picrotoxin and strychnine were administered subcutaneously (s.c.) and lidocaine was administered intraperitoneally (i.p.).

**Electroshock Apparatus**

In the electroshock experiments, a standard 60 Hz electroshock apparatus (Woodbury and Davenport, 1952) was employed for delivering 0.2 second pulses via corneal electrodes.

**Experimental Design**

The experiments were designed to obtain the following data in animals treated with either 30 mg/kg Δ9-THC or vehicle: median convulsant current (CC50); median convulsant dose (CD50); and median lethal dose (LD50).

The CC50 is a measure of the level of current which will produce convulsions in 50% of the animals. The CD50 and LD50 are measures of the dose of a drug required to produce convulsions or lethality, respectively, in 50% of the animals.
The maximal electroshock seizure threshold (MEST) was defined as the CC50 for maximal seizures while the threshold for minimal electroshock seizures (EST) was defined as the CC50 for minimal seizures.

In order to obtain these parameters, the following procedures were used. In electroshock tests, current-effect curves, each having 3 to 6 points, were graphed with each point representing the results obtained from 10 animals. In chemoshock and lethality studies, dose-effect curves each having 3 to 6 points were graphed, again with each point representing the results from 10 animals (see Figure 1, page 14).

CC50s and CD50s were measured for both maximal and minimal seizures. Definition of these seizure endpoints were as follows: maximal seizures were a continuous tonic extension of the hindlimbs for not less than 3 seconds; minimal seizures were a continuous clonus of the forelimbs lasting for 5 seconds or longer. Protection against seizures was defined as the prevention of these convulsive endpoints. Observations for seizure endpoints were made in a sound attenuated room for at least 1 1/2 hours following injection of the convulsant with the rats caged individually during this period. In addition, observations of the numbers of deaths and survivors of rats, caged individually in a sound attenuated room, were made for 24 hours following injection of the convulsant.
All experiments were conducted between the hours of 1000 and 1400 hours.

**Statistical Procedures**

The method of Litchfield and Wilcoxon (1949) was used for determining the CC50s, CD50s, along with 95% confidence limits (95% C.L.), from the current-effect and dose-effect curves. Tests for heterogeneous data and parallelism between curves were also done using this same method.

In animals treated with the 30 mg/kg of Δ9-THC, a CD50 could not be obtained for maximal PTZ seizures. This was due to the near total protection produced by this dose of Δ9-THC against this type of seizure. Furthermore in the experiments with picrotoxin the dosage range between 0% and 100% seizures was extremely narrow so that a CD50 could not accurately be determined. Nevertheless, for both of these conditions (PTZ and picrotoxin) the percent of seizures for each dose of convulsant was recorded.
CHAPTER 3

RESULTS

The results of these experiments are divided into three categories: the effects of Δ9-THC on procedures inducing maximal seizures; its effects on procedures inducing minimal seizures; and its effects on the lethality of animals given the four chemical convulsants. These results are displayed in Tables 1, 2, and 3 respectively.

In vehicle treated rats both maximal and minimal seizures were produced by electroshock and PTZ, only maximal seizures by strychnine, and only minimal seizures by lidocaine and picrotoxin.

Effects of Δ9-THC on Maximal Seizures

Electroshock

Initial experiments were conducted to measure the effect of Δ9-THC on seizures elicited by a supramaximal electroshock current (MES). In these experiments doses of 7.5, 15, and 30 mg/kg of Δ9-THC were used. These doses produced 20, 60 and 80 percent protection respectively, against MES. The ED50 and 95% C.L. calculated from these data was 19 mg/kg (10.5-34.2 mg/kg). The ED80 and corresponding 95% C.L. was 30 mg/kg (11.4-79.2 mg/kg).
TABLE 1

Effects of Δ9-tetrahydrocannabinol (Δ9-THC) and Δ9-THC vehicle (V) pretreatment on electroshock (MEST), strychnine, and pentylenetetrazol (PTZ) induced maximal seizures.

<table>
<thead>
<tr>
<th></th>
<th>MEST&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Strychnine&lt;sup&gt;1&lt;/sup&gt;</th>
<th>PTZ&lt;sup&gt;2&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Sulfate</td>
<td>70</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(mg/kg)</td>
</tr>
<tr>
<td>V</td>
<td>70 mA</td>
<td>1.78 mg/kg</td>
<td>10%</td>
</tr>
<tr>
<td></td>
<td>(51.8-94.5)</td>
<td>(1.5-2.12)</td>
<td></td>
</tr>
<tr>
<td>Δ9-THC</td>
<td>630 mA</td>
<td>1.78 mg/kg</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>(352-1130)</td>
<td>(1.5-2.12)</td>
<td></td>
</tr>
</tbody>
</table>

<sup>1</sup>Numbers represent median convulsant currents (CC<sub>50</sub>'s) for MEST and median convulsant doses (CD<sub>50</sub>'s) for strychnine, given subcutaneously; numbers in parentheses are 95% confidence limits. Each median value represents data from 30-60 rats.

<sup>2</sup>Percentages represent the percentage of animals exhibiting convulsions at various doses of PTZ, given subcutaneously; data obtained from 10 rats per dose condition, i.e., a total of 60 animals.

<sup>3</sup>Dose of 30 mg/kg, given orally.
TABLE 2

Effects of \( \Delta 9 \)-tetrahydrocannabinol (\( \Delta 9 \)-THC) and \( \Delta 9 \)-THC vehicle (V) pretreatment on electroshock (EST), pentylenetetrazol (PTZ), lidocaine and picrotoxin induced minimal seizures.

<table>
<thead>
<tr>
<th></th>
<th>EST(^1)</th>
<th>PTZ(^1)</th>
<th>Lidocaine(^1) Hydrochloride</th>
<th>Picrotoxin(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.10 1.75 4.00</td>
</tr>
<tr>
<td>V</td>
<td>19 mA</td>
<td>47 mg/kg</td>
<td>70 mg/kg</td>
<td>20% 80% 100%</td>
</tr>
<tr>
<td></td>
<td>(17.8-20.3)</td>
<td>(43.1-51.2)</td>
<td>(60.9-80.9)</td>
<td></td>
</tr>
<tr>
<td>( \Delta 9 )-THC(^3)</td>
<td>18.8 mA</td>
<td>47 mg/kg</td>
<td>66 mg/kg</td>
<td>0% 80% 100%</td>
</tr>
<tr>
<td></td>
<td>(18.0-19.6)</td>
<td>(43.1-51.2)</td>
<td>(51.2-85.0)</td>
<td></td>
</tr>
</tbody>
</table>

\(^1\)Numbers represent median convulsant currents (CC\(^50\)s) for EST and median convulsant doses (CD\(^50\)s) for PTZ given subcutaneously and lidocaine given intraperitoneally; numbers in parentheses are 95% confidence limits. Each median value represents data obtained from 30-60 rats.

\(^2\)Percentages represent the percent of animals exhibiting convulsions at various doses of picrotoxin given subcutaneously; data obtained from 10 rats per dose condition, i.e., a total of 60 animals.

\(^3\)Dose of 30 mg/kg, given orally.
TABLE 3

Median lethal doses (LD50's) of pentylenetetrazol (PTZ), lidocaine, strychnine and picrotoxin following pretreatment with Δ9-tetrahydrocannabinol (Δ9-THC) and Δ9-THC vehicle (V).

<table>
<thead>
<tr>
<th></th>
<th>PTZ²</th>
<th>Lidocaine³</th>
<th>Strychnine⁴</th>
<th>Picrotoxin⁵</th>
</tr>
</thead>
<tbody>
<tr>
<td>V</td>
<td>79</td>
<td>116</td>
<td>1.78</td>
<td>3.0</td>
</tr>
<tr>
<td></td>
<td>(70.0-89.8)</td>
<td>(98.3-136)</td>
<td>(1.50-2.12)</td>
<td>(2.6-3.4)</td>
</tr>
<tr>
<td>Δ9-THC¹</td>
<td>79</td>
<td>115</td>
<td>1.78</td>
<td>3.4</td>
</tr>
<tr>
<td></td>
<td>(70.0-89.8)</td>
<td>(103-127)</td>
<td>(1.50-2.12)</td>
<td>(2.8-4.0)</td>
</tr>
</tbody>
</table>

Numbers are mg/kg and numbers in parentheses represent 95% confidence limits. Each value represents data from 30-60 animals.

¹Dose of 30 mg/kg, given orally.
²Dose given subcutaneously.
³Dose calculated as lidocaine hydrochloride, given intraperitoneally.
⁴Dose calculated as strychnine sulfate, given subcutaneously.
⁵Dose given subcutaneously.
The effect of two doses of Δ⁹-THC on maximal electroshock seizure threshold (MEST) is shown in Figure 1. The values for MEST in milliamperes (mA) along with their 95% C.L. were: 70 mA (51.8-94.5 mA) for vehicle; 200 mA (125-320 mA) for 15 mg/kg Δ⁹-THC; and 630 mA (352-1130 mA) for 30 mg/kg Δ⁹-THC. Thus a dose of 15 mg/kg increased MEST to slightly more than 2.8 times the control level (Figure 1) while a dose of 30 mg/kg increased the threshold to 9 times the control value (Figure 1 and Table 1). The differences in MEST following these three treatments are all significant (p<0.05). Table 1 gives a comparison of the effect of 30 mg/kg Δ⁹-THC on MEST with the effect on PTZ and strychnine seizures.

Further, a preliminary study demonstrated an increase in threshold in rats to maximal seizures induced by 6-Hz stimulation following a comparatively low (10 mg/kg) oral dose of Δ⁹-THC. At this dose, the threshold for 6-Hz MEST was raised from 64 millivolts (mV) (54.2-75.5 mV, 95% C.L.) for vehicle to 90 mV (72.6-111.6 mV, 95% C.L.) for Δ⁹-THC treated animals. This difference, while small, was nevertheless statistically significant (p<0.05).

Pentylenetetrazol

Doses of PTZ in the lethal range (70-100 mg/kg) produced a high incidence of maximal seizures in control animals (CD50=88 mg/kg, 95% C.L., 77.8-99.4 mg/kg). As can be
Figure 1. Effect of oral 9-tetrahydrocannabinol (9-THC) and 9-THC vehicle on the threshold (milliamps or mA) to maximal electroshock seizures.
seen in Table 1, a CD50 could not be obtained for PTZ in animals pretreated with 30 mg/kg of Δ9-THC. The data clearly show that Δ9-THC protects against maximal PTZ seizures.

**Strychnine**

In contrast to maximal electroshock and PTZ seizures, Δ9-THC did not alter the strychnine induced maximal seizures as shown by the identical CD50's for Δ9-THC and vehicle treated animals (Table 1).

**Effects of Δ9-THC on Minimal Seizures**

**Electroshock, Pentylenetetrazol, and Lidocaine**

Table 2 shows the CC50's for minimal electroshock seizure threshold (EST) and the CD50's for PTZ and lidocaine induced minimal seizures. As indicated by the similarity of median values for vehicle and Δ9-THC pretreated rats, Δ9-THC does not protect against electroshock, PTZ or lidocaine induced minimal seizures (p>0.95).

**Picrotoxin**

As previously mentioned, the dosage range between 0% and 100% convulsant effects with picrotoxin was too narrow to accurately determine a CD50. From Table 2 it is apparent however that Δ9-THC produced no evidence of protection over the 3 doses of picrotoxin used.
Effects of Δ9-THC on Lethality

A comparison of lethality, i.e., LD50's, induced by PTZ, lidocaine, strychnine, or picrotoxin following pretreatment by vehicle and by Δ9-THC (30 mg/kg) is shown in Table 3. Clearly, Δ9-THC did not affect the LD50's for the four drugs used (p>0.95). Moreover, in the case of PTZ and strychnine, the LD50's were identical for vehicle and Δ9-THC pretreated animals.
CHAPTER 4

DISCUSSION

Results of the present study confirm and extend findings from other studies of the effects of \(^9\)-THC on minimal and maximal seizures and lethality of chemical convulsants.

The data of the present electroshock study are in agreement with earlier reports (Consroe and Man, 1973; McCaughran et al., 1974) showing \(^9\)-THC to protect against maximal electroshock seizures in rats. The present results indicate that \(^9\)-THC produces a dose-related elevation of MEST and a dose-related increase in percent protection against MES.

In contrast to many effects of \(^9\)-THC that often vary with differences in species, protection by this drug against MES is demonstrable across species. Thus, in addition to studies in rats, protection has been shown in mice (Fujimoto, 1972; Garriott, Forney, Hughes and Richards, 1968; Karler et al., 1973, 1974a, 1974b, 1974c; Sofia et al., 1971) and frogs (Karler et al., 1974d). From these studies it is apparent that protection against MES is a well established effect of \(^9\)-THC.

Curiously however, two studies have reported a lack of protection by \(^9\)-THC against MES in mice (Chesher and
Jackson, 1974; Dwivedi and Harbison, 1975). Dwivedi and Harbison (1975) reported a lack of protection 1 hour following i.p. administration of Δ9-THC, although doses used in this study were not specified. This reported lack of effect may be due to dose or possibly to testing time since Karler et al. (1973) demonstrated the peak effect time in mice for protection against MES following i.p. administration to be 2 hours. Another study (Chesher and Jackson, 1974) has reported very little protection at 1, 2, 3, and 4 hours following oral administration of Δ9-THC over a number of doses.

One explanation for the lack of protection in both of the above studies may be made on the basis of dose. Since doses were not specified in the first study however it is only possible to discuss the results of the latter study (Chesher and Jackson, 1974). In regards to this, Karler et al. (1974a) have shown that the ED50 against MES following i.p. injection of Δ9-THC is much higher for mice (101 mg/kg) than for rats (4.3 mg/kg). Using these values and values from the present study some approximate calculations can be made. In the present study in rats, the p.o. ED50 for Δ9-THC against MES (19 mg/kg) was 4.5 times the i.p. ED50 for rats (4.3 mg/kg) as measured by Karler et al. (1974a). However the highest p.o. dose used in mice in the study by Chesher and Jackson (1974) was 200 mg/kg or only 2 times the i.p. ED50 for mice as reported
by Karler et al. (1974a). At this latter dose 4 out of 10 mice were protected against MES. In contrast to the conclusion of Chesher and Jackson (1974) that this "high" dose of $\Delta 9$-THC appeared to show little protection, it is apparent from the above that 200 mg/kg is probably a rather low oral dose in mice for protection against MES. Indeed the 4 out of 10 mice protected at this dose further illustrates the effectiveness of $\Delta 9$-THC in this seizure model. Interestingly, in the same study (Chesher and Jackson, 1974), the authors demonstrated that a dose of only 100 mg/kg of $\Delta 9$-THC protected mice against MES lethality.

Prevention of maximal seizures induced by PTZ was also evident in the present study following a 30 mg/kg oral dose of $\Delta 9$-THC, a dose (i.e., ED80) which clearly provided protection against MES. This result is in agreement with previous findings showing protection against maximal PTZ seizures when rats were given i.v. $\Delta 9$-THC prior to PTZ infusion (Consroe and Man, 1973), and is consistent with data in mice showing i.p. $\Delta 9$-THC to produce some protection against maximal PTZ seizures (Turkanis et al., 1974). Data from the latter study however also serve to demonstrate that, as with MES, a higher dose of $\Delta 9$-THC is required to provide protection in mice than rats. These investigators showed that a 300 mg/kg dose, or 3 times the ED50 for MES in mice, provided only 50% protection
in mice against maximal PTZ seizures. In the present study in rats a dose of 30 mg/kg equal to 1.6 times the ED50 for MES provided almost total protection against PTZ maximal seizures.

Thus there appears to be quantitative differences across species in susceptibility to protection against MES and PTZ seizures. Nevertheless, some degree of protection by Δ9-THC has been shown for these two seizure models in both of the species (rats and mice) which have been widely tested.

The finding in the present study that Δ9-THC does not alter the CD50 for strychnine maximal seizures is in contrast to an earlier study which reported an enhancement of strychnine seizures with Δ9-THC (Sofia et al., 1971). Both of these findings demonstrate however that protection against maximal seizures by Δ9-THC is not a general effect but rather that Δ9-THC exhibits a specificity of action based on the type of maximal seizure involved.

In contrast to its effects against MES and PTZ maximal seizures, Δ9-THC in the present study did not protect against minimal seizures induced by electroshock (60-Hz), PTZ, picrotoxin, or lidocaine. This lack of protection against minimal seizures is consistent with other studies in rats (Consroe and Man, 1973) and mice (Karler, 1973; Karler et al., 1974a). However a study by Karler et al. (1974a) did demonstrate a protective effect of Δ9-THC
against minimal seizures induced by 6-Hz electroshock. Thus, as with maximal seizures, Δ9-THC demonstrates a specificity of action based on the type of minimal seizure involved.

Previous studies in rats have shown a lack of protection (Consroe and Man, 1973) or at best partial protection (McCaughran et al., 1974) against minimal PTZ seizures. In the latter study, doses of Δ9-THC which protected against MES provided only slight protection against minimal PTZ seizures and significant protection was obtained only at a lethal dose Δ9-THC.

It should be pointed out that results of the present and other studies in rats on PTZ minimal seizures are at variance with previously reported data in mice. Thus in mice both potentiation (Sofia et al., 1971; Karler et al., 1974a) and protection (Dwivedi and Harbison, 1975) of these seizures have been shown.

Lethality induced by PTZ, lidocaine, strychnine, or picrotoxin was shown in the present study to be unaffected by an anticonvulsant dose of Δ9-THC. A previous study in rats (Consroe and Man, 1973) demonstrated lack of protection against PTZ lethality by a dose of Δ9-THC which blocked MES. Interestingly, a recent study in mice (Dwivedi and Harbison, 1975) demonstrated protection against PTZ lethality by Δ9-THC at an oral dosage range of 12.5-50 mg/kg. As was previously mentioned, this is probably a very
low dosage range for anticonvulsant activity in mice. However Sofia et al. (1971) reported a potentiation of PTZ lethality by Δ9-THC in mice. Thus as was the case with PTZ minimal seizures, the effect of Δ9-THC on PTZ lethality in mice has produced equivocal results while results in rats on this effect have been consistent. This difference in results may be due to a strain difference in mice or a species difference between rats and mice.

In regards to its effect on strychnine lethality Δ9-THC provides no protection. Results of the present study in rats are in agreement with previous reports of lack of protection by Δ9-THC in mice (Sofia et al., 1971; McCoy, Brown, and Forney, 1974) against strychnine lethality.

The protection by Δ9-THC against maximal electroshock and maximal PTZ seizures, as well as the lack of protection against strychnine maximal seizures and minimal electroshock, PTZ, and picrotoxin seizures, describes a spectrum of activity similar to that of phenytoin, i.e., diphenylhydantoin (DPH), in respect to these types of convulsions (Woodbury, 1969). The lack of protection by Δ9-THC against lidocaine induced seizures is also similar to the reported inability of DPH to block this type of seizure (deJong, 1970). In a similar vein, DPH does not prevent lethality induced by PTZ, strychnine (Sofia et al., 1971) or lidocaine (deJong, 1970).
Thus, the present study demonstrates an anticonvulsant spectrum for Δ9-THC qualitatively similar to that of DPH and by implication suggests a similar mechanism of action. In support of this hypothesis, it is known that DPH raises the threshold for minimal seizures produced by 6-Hz electroshock (Woodbury, 1969) and this same effect has been shown for Δ9-THC (Karler et al., 1974a). Also Turkanis and Karler (1975) have reported recently that 11-OHΔ9-THC, a metabolite of Δ9-THC, blocks post-tetanic potentiation, a well known action of DPH (Woodbury, 1969). Another study (Izquierdo and Orsingher, 1973) has suggested interference by Δ9-THC with hippocampal potassium release following afferent bombardment and this same effect was shown for DPH. These latter two studies appear to provide evidence at a cellular level for similar mechanism of action of these two anticonvulsants.

Further support for this similarity comes from a study by Karler et al. (1974c) which demonstrated cross tolerance between Δ9-THC and DPH. From all these studies it is apparent that there is ample evidence suggesting Δ9-THC resembles DPH in its pharmacological mechanism of action.
CHAPTER 5

SUMMARY AND CONCLUSION

1. Δ9-THC, given orally, provides anticonvulsant activity against maximal electroshock and maximal chemoshock seizures induced by pentylenetetrazol.

2. Maximal seizures induced by strychnine and minimal seizures induced by electroshock, pentylenetetrazol, lidocaine or picrotoxin are not prevented by an oral dose of Δ9-THC which is the ED80 against MES (30 mg/kg).

3. Lethality induced by pentylenetetrazol, strychnine, lidocaine, or picrotoxin is not affected by an oral dose of Δ9-THC at 30 mg/kg.

4. The spectrum of anticonvulsant activity of Δ9-THC in the present study is similar to the previously reported data on the spectrum of activity of phenytoin. This suggests a similar mechanism of action of these two drugs.
REFERENCES


