TETRAHYDROCANNABINOL EFFECTS ON EXTRAPYRAMIDAL MOTOR BEHAVIORS IN AN ANIMAL MODEL OF PARKINSON'S DISEASE*

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I. INTRODUCTION

Although delta-9-tetrahydrocannabinol (THC) and related cannabinoids have been studied for several years, no clear functional relationship between a specific neurotransmitter effect and an important influence on behavior has been discovered. The key to understanding the functional effect of cannabinoids on behavior would require that: 1) the neuroanatomical substrate for the behaviors being studied must be relatively known, 2) the neurotransmitters interacting in the system must be at least partially identified, and 3) the behavior being studied should be very sensitive to cannabinoid effects as well as easily and reliable measured. A behavioral model which meets the above criteria and which may be useful in elucidating behaviorally significant neurotransmitter effects of the cannabinoids is the reserpine animal model of Parkinson's disease. In this model, monoamines in the extrapyramidal system are depleted by pretreatment with reserpine.

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The resulting behavioral syndrome includes the classic Parkinsonian symptoms of muscular rigidity and hypokinesia (1). These behavioral effects are easily and reliably measured as well as exquisitely sensitive to cannabinoid effects (2).

Creveling et al. have established that the main symptoms of rigidity and hypokinesia observed in the reserpine syndrome are due to depletion of dopamine, as in Parkinson's disease (3). For example, these investigators were able to demonstrate a dramatic "awakening" of reserpinized animals by administration of L-DOPA but not by 3,4-dihydroxyphenylserine, a compound decarboxylated directly to norepinephrine in the brain. In addition, Anden and Johnels found that apomorphine, a dopaminergic agonist, injected directly into the corpus striatum (caudate/putamen) and related extrapyramidal areas of reserpine-treated rats caused a marked reduction in reserpine-induced rigidity and hypokinesia (4). Furthermore, because of the extensive studies of extrapyramidal disorders, the neurotransmitters that interact with the major dopamine systems related to the control of extrapyramidal motor behaviors are relatively well known. These include very important interactions between dopamine and acetylcholine, gamma-aminobutyric acid (GABA), glutamic acid, 5-hydroxytryptamine, norepinephrine, and other minor neurotransmitters (for reviews, see 5-7). The reserpine syndrome, as an animal model of Parkinson's disease, is therefore, relatively well understood particularly with regard to the origin of the symptoms of hypokinesia and rigidity.

II. EXPERIMENTS AND RESULTS

A. Experiment 1. The Effects of THC and Other Cannabinoids on Reserpine-induced hypokinesia in a Model of Parkinson's Disease

In view of the information regarding the origin of the behavioral effects observed in the reserpine syndrome, it was of particular interest that Moss, McMaster and Rogers reported that THC produces a remarkable potentiation of reserpine-induced hypokinesia in the rat (2). In these experiments, rats were pretreated with 7.5 mg/kg reserpine 24 hours prior to behavioral tests for hypokinesia. In addition, part of these animals were also give 10 mg/kg THC by gavage 4 to 5 hours before the behavioral tests. This method of THC administration was selected because it produces a large and reliable decrease in rectal temperature that peaks at 4 to 5 hours after administration (8). In these experiments, reserpine-induced hypokinesia was measured by the bar test (2,9). In

the bar test, the rat is placed with its front paws resting on a small horizontal rod (i.e., a "bar") elevated 9 cm above a small platform upon which the rear paws are placed. The bar test simply measures the amount of time required for the animal to get down from the bar. It is a very reliable measure of unwillingness or inability to move (i.e., hypokinesia). As shown in Figure 1, control animals (i.e., undrugged animals that received vehicle only) and animals treated only with THC remove themselves from the bar with an average time of less than 3 seconds. The bar test results obtained with reserpine, however, show significant hypokinesia with an average bar time of about 40 seconds. This hypokinesia was expected as one of the Parkinsonian-like symptoms observed in this animal model. The most striking results were obtained, however, when animals were given both reserpine and THC. In this case, the animals required an average of more than 15 minutes to remove themselves from the bar. Insofar as an arbitrary maximum time of 30 minutes was allowed for the bar test, this effect was partially limited by a ceiling effect. Although muscular rigidity was not objectively measured in these experiments, informal observations suggested that there was no difference between reserpine-alone pretreated rats and THC/reserpine pretreated rats with regard to this particular reserpine-induced

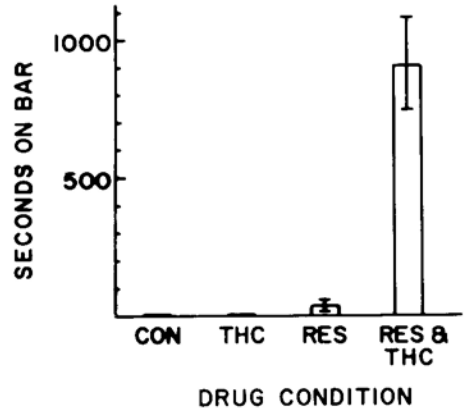

FIGURE 1. Effect of THC (10 mg/kg) on reserpine-induced hypokinesia. Comparison of the reserpine treated animals (RES) and the THC/reserpine treated animals (RES & THC) shows the magnitude of the THC potentiation of reserpine-induced hypokinesia. All groups contained 8 animals and the error bars represent one SEM. The main effect of RES and the interaction between RES and THC were both highly significant ($p < 0.001$). [Reproduced from Moss et al. (2) with permission].

effect. In spite of the severe hypokinesia observed in these tests, the THC/reserpine treated animals were able to show immediate and well organized righting reflexes as well as locomotor responses to footshock.

Using the same procedures reported above, the effects of 10 mg/kg (orally by gavage) of cannabichromene, cannabidiol, and levonantradol, a synthetic analog of THC, on reserpine-induced hypokinesia were also studied in the rat. Cannabichromene had no detectable effect, cannabidiol was less potent than THC, and levonantradol was extremely powerful relative to THC. In fact, all 6 of the animals tested with the combination of levonantradol and reserpine stood motionless at the bar for the maximum recorded time of 30 minutes. Actually, some of the animals remained on the bar more than an hour and one exceeded 2 hours.

Because of the extreme interaction observed between THC and reserpine in the rat as described above, it was important to determine if this effect could be expected in primates as well as rodents, and furthermore, to determine if THC would potentiate the hypotensive effect of reserpine. The latter effect, if it occurred, could have significant health-related potential. Therefore, a 15 Kg male 12 year old stump tailed macaque (M. arctoides) was trained to present his arm to the experimenters for food reward so that his blood pressure could be measured using a sphygmomanometer. A predrug baseline systolic and diastolic pressure was established at 138/78 mm Hg (S.E.M. = 5 mm Hg). Thereafter, the monkey was given increasing doses of reserpine orally twice a day until a drop in both systolic and diastolic pressures were observed. Thedose determined by this procedure was 2 mg/kg, which caused a peak drop in blood pressure to 86/44 mm Hg (S.E.M. = 7 mm Hg)3 hours after the reserpine. THC was then administered orally (1 mg/kg) in an oil solution on a cookie at the beginning of the reserpine-induced hypotension and blood pressure was measured regularly for the following 7 hours. THC had no reliable effect on reserpine-induced hypotension and, in addition, there were no differences observed 24 hours later on the first drug-free recovery day following each replication of the experiment.

Even though there were no differences in blood pressure produced by adding THC to reserpine, there were very clear behavioral differences that corroborate the effects observed earlier in rats. In the no drug condition, this monkey was very active and aggressive. With 2 mg/kg reserpine, he was much less active and was generally cooperative and submissive. When THC was added to the reserpine treatment, however, he became very unresponsive and cataleptic (i.e., he spentseveral periods of an hour or longer in peculiar positions without movement). He frequently sat with his face propped into

the corner of his cage. One time he hung upside down by all four feet from the top of his cage for well over an hour without moving. In the THC/reserpine condition, he could be rolled out of his cage and positioned for his blood pressure measurements. Because of his extreme cataleptic condition, he would maintain positions established by the experimenters for long periods of time. The behavioral effects of adding THC to reserpine were quite dramatic and none of these peculiar behaviors were ever observed in the THC-alone or reserpine-alone conditions.

The results obtained in Experiment 1 show that THC greatly increases reserpine-induced hypokinesia in rats and primates. However, THC does not increase all effects of reserpine insofar as THC had no detectable effect on reserpine-induced hypotension.

B. Experiment 2. Dose Response and Time Course of the THC Effect in Reserpinized Rats

In order to obtain more information about the THC/reserpine-induced hypokinesia observed in Experiment 1, this experiment was conducted to determine the effect of dose of THC and the duration of its potentiation of reserpine hypokinesia. Figure 2 shows that THC potentiation of reserpine-induced hypokinesia, in fact, follows a well defined time course. In this experiment, 7.5 mg/kg reserpine was administered 24 hours before the bar test for all animals. The administration of THC was, however, varied so that it preceded the bar test in each independent group by the time shown in the figure. The bar tests were conducted at the same time of day for all groups to control for possible circadian effects on behavior. Figure 2 also shows that THC/reserpine hypokinesia is dependent on the dose of THC administered up to 10 mg/kg, the highest dose tested in these experiments. It is interesting to note that the time course of the THC effect revealed in these experiments on motor behaviors is similar to the time course reported for the euphoric effects of marijuana after oral administration in humans (10). In addition, because of the distinct time course revealed in this experiment, it appears that THC might be producing its motor effects observed in these experiments through a specific and well defined neurotransmitter effect.

C. Experiment 3. The Effect of Administering Reserpine after THC-Pretreatment

In the experiments reported above, reserpine was always

administered 24 hours prior to the behavioral tests so that the behavior was studied during a steady state of monoamine depletion. Fischer and Heller also observed that the behavioral effects of reserpine develop shortly after injection and remain unaltered for longer than 24 hours and then gradually diminish to a practically normal state by 48 hours (11). However, if THC was having its effect by alteration of the rate of turnover of affected neurotransmitters or the rate or extent of depletion, there might be a significantly different effect early in the development of the reserpine syndrome. Therefore, the effect of THC on reserpine-induced hypokinesia was studied at a constant 4 to 5 hours after THC administration as in the above experiments but only two hours after reserpine administration. The results were quite remarkable. Although the reserpine-alone animals showed severe hypokinesia and rigidity, the THC/reserpine treated animals showed a much more extreme effect. Bar tests were not administered because their bodies were so rigidly fixed in a curled posture (e.g., a "bean" appearance) that it was impossible to place them on the bar. The THC/reserpine treated animals showed no righting reflex and showed no response when their rigid bodies were tapped gently on a table. This extreme effect lasted only between 2 and 3 hours after reserpine administration. The results of this experiment emphasized the importance of examining the effect of THC on reserpine-induced depletion of the monoamines.

D. Experiment 4. The Effects of THC on Reserpine-Induced Monoamine Depletion

In this experiment, rats were pretreated with reserpine and THC exactly in accordance with the procedures used in the first THC/reserpine experiments reported above. Specifically, the animals were pretreated with reserpine (7.5 mg/kg) or a placebo control injection either 2 or 24 hours prior to being sacrificed for biochemical analysis of the caudate/putamen. in addition, half of the reserpine pretreated and half of the control animals were further treated with 10 mg/kg THC by gavage approximately 4 hours before being sacrificed. There were 8 animals in all drug conditions. All animals were also given tests for hypokinesia immediately before sacrifice in order to confirm that the biochemical data were collected during the extreme behavioral effects observed earlier. The animals were then decapitated, the brain was rapidly removed and cooled, and the caudate/putamen dissected out of the brain. The caudate/putamen was then rapidly frozen on dry ice and maintained frozen until analysis. The monoamines and two related metabolites were separated by high performance liquid

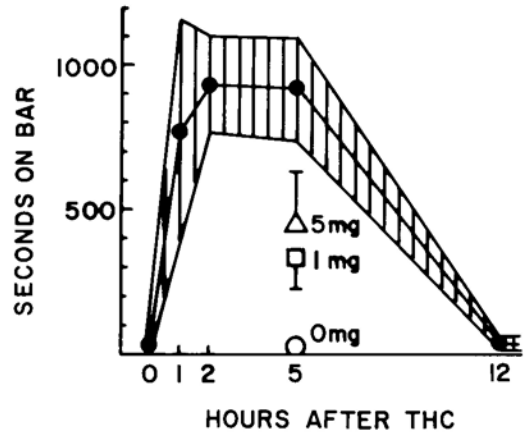

FIGURE 2. Dose- and time-dependence of THC effect on reserpine-induced hypokinesia. All animals were pretreated with 7.5 mg/kg reserpine. The shaded area (mean +/- SEM) represents the time-dependent effect at 10 mg/kg THC. The open symbols at 5 hours show the effect of various doses of THC. Animals were tested at only one time or dose group. The results obtained at 24 hours were identical to those obtained at 0 and 12 hours and are, therefore, not shown. All groups contained 4 animals except those at 5 hours which contained8 animals. The effects of time and dose were both highly significant ($p < 0.01$). [Reproduced from Moss et al. (2) with permission].

chromatography and quantified by electrochemical detection. Dopamine, norepinephrine and the dopamine metabolite 3,4-dihydroxyphenylacetic acid (DOPAC) were assayed according to the procedure of Steger, Bartke and Goldman (1982). 5-Hydroxytryptamine and the metabolite 5-hydroxyindoleacetic acid (5-HIAA) were measured according to the method of Steger and Bartke (12,13). The results are shown in Figures 3 and 4.

Figures 3 and 4 demonstrate that THC has no effect on reserpine induced depletion of the monoamines in the caudate/putamenat either 2 or 24 hours after reserpine. The finding that there was no apparent effect of THC at either 2 or 24 hours after reserpine and, in addition, THC had no effect on the content of DOPAC and 5-HIAA suggests that THC also probably did not affect turnover rates of the monoamines being studied.

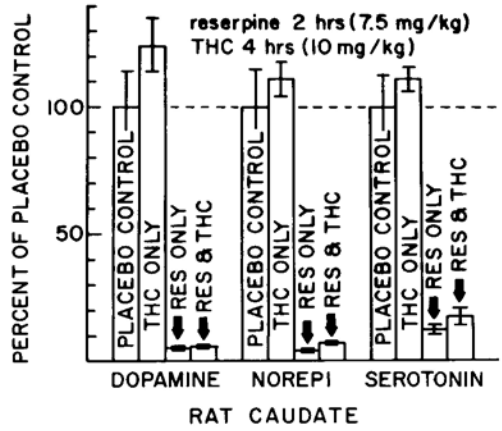

FIGURE 3. The effects of reserpine (RES) and THC on rat caudate/putamen monoamine content at 2 hours after reserpine. The THC and/or reserpine treated animals received THC (10 mg/kg) 4 hours and/or reserpine (7.5 mg/kg) 2 hours prior to being sacrificed for assays. The 100% control values taken from placebo treated animals are 6194 ng/gm dopamine, 2602 ng/gm norepinephrine, and 450 ng/gm 5-hydroxytryptamine. There were 8 animals in each group and the error bars represent one SEM.

E. Experiment 5. The Effects of THC on Haloperidol- and Chlorpromazine-induced Hypokinesia

Insofar as THC had no apparent effect on monoamine depletion induced by reserpine, an additional experiment was conducted to determine if hypokinesia induced by other, more specific dopaminergic antagonists is also increased by concurrent administration of THC. These results, obtained with haloperidol (a representative butyrophenone) and chlorpromazine (a representative phenothiazine), are shown in Figure 5. It is interesting to note the striking difference between the effects of THC on the hypokinesia induced by these two dopaminergic antagonists. Although the reason for the difference in the effects observed with these two compounds is completely obscure, it may be due to the alpha-adrenergic effect of the chlorpromazine which is largely absent in the haloperidol (14).

In spite of the inconsistent effect obtained with chlorpromazine in this experiment, our working hypothesis is that the THC influence on extrapyramidal motor function is normally

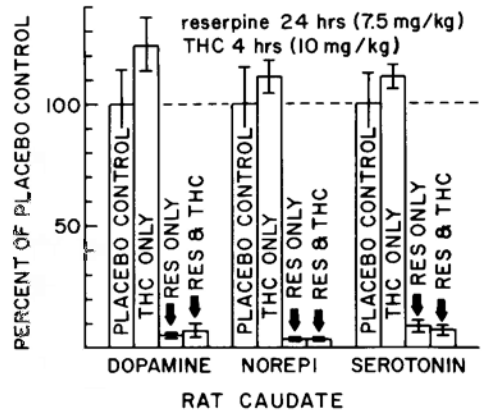

FIGURE 4. The effect of reserpine (RES) and THC on rat caudate/putamen monoamine content 24 hours after reserpine. The THC and/or reserpine treated animals received reserpine (7.5 mg/kg) 24 hours and/or THC (10 mg/kg) 4 hours prior to being sacrificed for assays. This experiment was conducted concurrently with that shown in Fig. 3 and, therefore, the 100% values determined in the undrugged control animals are the same for Figs. 3 and 4. There were 8 animals in each group and the error bars represent on SEM.

a minor subtle effect, probably on a nondopaminergic system, that is masked by the function of the major extrapyramidal dopamine system. In the absence of the regulatory effect of the main dopamine system, however, the normally occult effect(s) of THC become observable.

F. Experiment 6. The Effects of THC on KCl-Induced Inactivation of the Striatum

The purpose of Experiment 6 was to determine if, in contradiction to the working hypothesis presented above, nonspecific inactivation of the striatum would be a sufficient condition for observing the THC effect on extrapyramidal motor behaviors. This was a particularly important experiment because of the earlier work by Gough and Olley (9).

Gough and Olley reported inducing "catalepsy" (hypokinesia) in rats by intracranial injection of THC and 11-OH-THC into the caudate/putamen of rats through chronically in-dwelling cannulae (9). In addition, they observed catalepsy in similarly prepared rats which received THC systemically even though no injections were made through the cannulae. Cata-

lepsy was never observed in control rats (i.e., not prepared with cannulae) when THC was administered systemically. This "cannula" effect, in particular, suggested that nonspecific disruption of striatal function is sufficient for THC-induced hypokinesia.

It is important to note that Gough and Olley used a bar test virtually identical to that used in our experiments except that they placed the rats on the bar once a minute for several minutes until catalepsy was observed (9). In contrast, in our experiments, the bar tests are separated by at least 30 minutes and administered a maximum of 3 times. In fact, some experiments we conducted suggested very strongly that the "catalepsy" observed by Gough and Olley (9) was due to learning to stand at the bar (for example, to avoid being handled, etc.) or some other nonspecific effect induced by excessive testing. However, the report of the "cannula" effect suggested that THC might produce hypokinesiawhenever striatal function was disrupted. In this case, the specific dopamine involvement suggested in our working hypothesis presented above might be unfounded. Therefore, Experiment 6 was completed to test the hypokinetic effect of THC when normal striatal function was disrupted by intracranial injection of KCl.

In this experiment, seven rats were prepared with chronically indwelling cannulae directed into the dorsal caudate/putamen according to the coordinates of Gough and Olley (9). In the first part of this experiment, the inactivation of the striatum by KCl injection was confirmed by the procedure of Anden and Grabowska-Anden (15). In this control experiment,each animal was injected intracranially with 1 mcl of 25% KCl on one side and an equimolar amount of NaCl (1mcl of 20%) simultaneously on the other side. Immediately following these intracranial injections, the animals were injected i.p. with apomorphine, a dopamine agonist. The extent to which the KCl injection inactivated the striatum was then measured behaviorally but the number of rotations observed during the next 45 minutes. In accordance with the desired effect of inactivating the striatum, after the first few minutes, all of the animals showed rotation ipsilateral to the KCl injection site.

The control experiment described above confirmed that the location of the cannulae and the injections of KCl were sufficient to produce nonspecific functional disruption of striatal function. In the second part of the experiment all animals were then injected bilaterally with 1 mcl of 25%KCl or, in the control condition, 1 mcl of 20% NaCl and tested for hypokinesia using the bar test procedure of Moss et al. (2). with and without an additional administration of 10 mg/kgTHC (gavage). All of the subjects were subjected to all condi

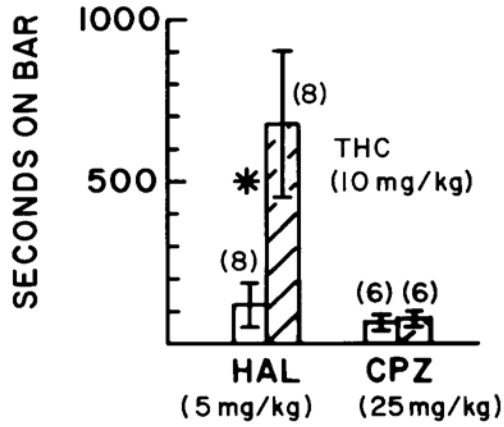

FIGURE 5. The effect of THC (10 mg/kg) on haloperidol (HAL) or chlorpromazine (CPZ) induced hypokinesia. THC or a placebo was administered 4 hours prior to and either HAL or CPZ was administered i.p. 30 minutes prior to the bar tests. The number of animals in each group is shown in parentheses and the error bars represent one SEM. The effect of THC on HAL-induced hypokinesia was significant ($p < 0.05$).

tions in a counterbalanced order so that they served as their own controls. In addition, the entire experiment was replicated so that there were two different observations taken on each animal in each drug condition. Tests under different drug conditions were separated by a minimum of one week. The animals were tested with THC placebo and NaCl intracranial injections (placebo control), 10 mg/kg THC and NaCl intracranial injections (THC only condition), THC placebo and KCl intracranial injections (KCl only condition), and 10 mg/kg THC and KCl intracranial injections (THC/KCl condition). The results of this experiment were very clear. There was no hypokinesia observed in the control condition, the KCl only condition, THC only condition, and, furthermore, there was no hypokinesia observed in the THC/KCl condition. The average bartimes for these four drug groups ranged from 7 to 14 seconds. After the behavioral data were collected, frozen section histologies were performed on all subjects and the locations of the cannulae were confirmed. This experiment demonstrated that nonspecific disruption of striatal function is not a sufficient condition for the observation of THC effects on extrapyramidal motor behaviors.

G. Experiment 7. The Interaction of Cholinergic Drugs with THC as Measured in Motor Behaviors

Because of the very important cholinergic/dopaminergic interactions in the striatum and the effects of cholinergic drugs on the symptoms of Parkinson's disease, the effects of cholinergic drugs on reserpine-alone and THC/reserpine-induced hypokinesia were tested in this model. The results showed that reserpine-alone and THC/reserpine hypokinesia could be only slightly enhanced by 0.5 mg/kg physostigmine salicylate, a dose sufficient to produce 80% inhibition of brain cholinesterase (Moss, unpublished experiments). Even though the effect of physostigmine on reserpine alone as well as THC/reserpine hypokinesia was statistically significant, the behavioral effect was not at all dramatic and appeared to be a small, strictly additive effect. In addition, the interaction of THC with the cholinergic system was further studied by determining if the THC/reserpine hypokinesia could be reduced or blocked by 2 mg/kg scopolamine HBr, a muscarinic receptor antagonist, and 30 mg/kg ethopropazine (Parsidol), an anticholinergic antiparkinsonian drug. The THC/reserpine hypokinesia was not significantly reduced by the traditional muscarinic antagonist scopolamine but it was dramatically reduced by the administration of ethopropazine (2). The results of these experiments are, therefore, in general agreement with the effects of cholinergic drugs on Parkinson's disease. Specifically, the symptoms of this disease are moderately exacerbated by physostigmine, relatively unchanged by scopolamine, and reduced fairly effectively by ethopropazine.

The results of the experiments reported above using cholinergic drugs suggests that the cholinergic system does not have a major functional role in mediating the effect of THC on these extrapyramidal motor behaviors. It should be pointed out, however, that the effect of relatively specific nicotinic drugs has not been tested in this model. Although some of the effects were statistically significant, the magnitude ofthe behavioral changes was only modest and apparently insufficient to explain the large effect of THC on reserpine-induced hypokinesia.

III. CONCLUSIONS

Although the purpose of these experiments was to conduct basic research into the mechanisms of action of the cannabinoids, the results reported may have some potential clinical significance. The profound effects of THC and levonantradol on extrapyramidal motor behaviors suggest that patients taking

monoamine depleting or dopamine blocking drugs, or those who are suffering Parkinson's disease might experience untoward effects from the use of marijuana. On the other hand, THC or a related cannabinoid might be used to increase the clinical efficacy of drugs used in hyperkinetic motor disorders. For example, reserpine was one of the first agents to be employed in the treatment of various hyperkinetic choreiform disorders (16), and it has been shown to be of benefit in tardive dyskinesia (17,18), and Huntington's disease (19,20). In addition, it is interesting to note that patients with torsion dystonia have mentioned that marijuana use produces therapeutic effects comparable to those obtained with diazepam, a drug used in the treatment of that disorder (21). It appears, therefore, that selected cannabinoids may have some therapeutic value in the treatment of certain motor disorders. The series of experiments reported here, however, suggests that the most productive direction for future research may be related to the effects of cannabinoids on gamma-aminobutyric acid and other amino acid neurotransmitters or peptides that have functional significance in extrapyramidal motor control.

In the research related to marijuana and the cannabinoids, there seems to be an increasing interest in determining a relatively specific mechanism of action. It also seems quite likely that a class of drugs like the cannabinoids will, in fact, be discovered to have many mechanisms of action related to their diverse effects. The main disadvantage of studying the effects of the cannabinoids in this animal model of Parkinson's disease is that the cannabinoids must be studied as an interaction with other drugs. The other behavioral effects of cannabinoids are, however, usually extremely subtle and difficult to measure reliably. On the other hand, the relatively complete understanding of this model of Parkinson's disease afforded by extensive research on the extrapyramidal motor diseases and the exquisite sensitivity of these behaviors to certain cannabinoids may provide an unusual opportunity to discover at least one mechanism of action of the cannabinoids that has important functional significance for the nervous system and behavior.

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