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EFFECTS OF 1-Δ^9-TETRAHYDROCANNABINOL, *dl*-AMPHETAMINE AND PENTOBARBITAL ON OXYGEN CONSUMPTION BY MOUSE BRAIN AND HEART HOMOGENATES*

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Abstract—Using a polarographic method (oxygen electrode), the effects of 1-Δ^9-tetrahydrocannabinol (an active constituent of marihuana), DL-amphetamine and pentobarbital were compared in regard to their action on oxygen consumption by mouse brain and heart homogenates. This study was unique in that the drugs were injected *in vivo*, while measurement of oxygen consumption was conducted *in vitro* for up to 8 hr. This allowed for the true active forms of these drugs—after normal biotransformation, if necessary—to exert the effects later measured. Pentobarbital was found to have no significant effect on cerebral or cardiac oxygen consumption. Both DL-amphetamine and 1-Δ^9-tetrahydrocannabinol caused significant stimulation of oxygen consumption in the brain and heart for up to at least 2·5 hr after administration. This could indicate that both drugs cause increased synthesis and utilization of high energy compounds (i.e. ATP) via oxidative phosphorylation in the two organs. However, DL-amphetamine and 1-Δ^9-tetrahydrocannabinol also induced limited depression of oxygen consumption in the brain and heart, respectively, at 8 hr after administration.

ALTHOUGH varying amounts of cannabinols and cannabinol-like derivatives have been found in marihuana, *trans*-Δ^9-tetrahydrocannabinol (Δ^9-THC) is believed to be the active constituent of the plant.[1] Recent investigations[2] have shown that Δ^9-THC, as well as Δ^8-THC, is probably converted to active 11-hydroxy metabolites and that these metabolites may be responsible for the myriad effects reported with previous marihuana research. Since little is known on the molecular mode of action of *trans*-Δ^9-THC, we decided to study the effects of Δ^9-THC on the oxygen consumption of cerebral and cardiac homogenates. At the same time, we compared these results with those obtained by identical tests with the central nervous system depressant, sodium pentobarbital, and the CNS stimulant, DL-amphetamine.

METHODS

Drug solutions. The synthetic 1-Δ^9-THC was supplied by the Center for Studies of Narcotic and Drug Abuse, National Institutes of Mental Health. It was received dissolved in ethanol, within sealed glass ampules. It was subsequently stored in the dark at $-10°$ until used. Test solutions of Δ^9-THC were prepared 24 hr before scheduled testing. The ethanol was evaporated under dry nitrogen gas, and the Δ^9-

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THC residue was suspended in saline along with three drops of Tween-80. This mixture was gently shaken in the cold room overnight. Each mouse in the Δ^9-THC test group was given a 1·0-ml intraperitoneal injection of the solution, containing a dose of 50 mg/kg of Δ^9-THC. This concentration produced behavioral changes characterized by ataxia, hyperreactivity to tactile and auditory stimuli, and depressed gross locomotor activity; recovery occurred within 3–4 hr. Controls for this group were given an equivalent volume of the saline Tween-80 vehicle.

DL-Amphetamine sulfate (Benzedrine) was supplied in liquid form by the Department of Pharmacy, Geisinger Medical Center, Danville, Pa. At a dosage of 10 mg/kg, it was injected intraperitoneally into a second group of mice. Behavioral changes produced included irritability, agitated gross locomotor activity, and hyperreactivity to tactile and auditory stimuli; recovery occurred by 4 hr. Pentobarbital sodium, at a dose of 100 mg/kg, was injected intraperitoneally into a third group. Behavioral changes observed included heavy sedation, absence of gross locomotor activity, and no reactivity to tactile or auditory stimuli; recovery occurred within 3–4 hr. Saline solution served as the control medium for both of these groups.

Procedure. Male Swiss albino mice (20–25 g) were used for all testing. Four time intervals were chosen: 0·5 hr, 1·5 hr, 2·5 hr and 8 hr. After one of the four scheduled intervals, the animals were sacrificed by vertebral dislocation. The whole brain, including the medulla, and the heart were removed, washed, minced and homogenized with a variable speed homogenizer/Teflon pestle apparatus in iced isolation medium. This medium consisted of 225 mM mannitol, 75 mM sucrose, 0·1 mM EDTA, pH 7·1. The homogenates were then centrifuged at 500 *g* for 10 min to remove (by sedimentation) nuclei, whole cells and debris. Finally, 0·6 ml of the supernatant was pipetted into a reaction vessel containing 2·0 ml of specific medium (45 mM mannitol, 15 mM sucrose, 40 mM KCl, 20 mM $MgCl_2$, 20 mM potassium phosphate buffer, 0·02 mM EDTA, pH 7·4). It took approximately 18 min from sacrifice to introduction of the first supernatant into the reaction vessel. The order of testing the two organs was reversed periodically to equalize any effects of aging on the preparations.

With modifications of procedures used by Ziegler *et al.*,[3] oxygen consumption was then measured polarographically with a Clark-type oxygen electrode apparatus and recorded on a millivolt recorder. All measurements were made at a constant temperature of 25·0 ± 0·1°. For each homogenate, four consecutive parameters (or rates) of normal and stimulated oxygen consumption were measured: (1) endogenous rate; (2) succinate rate, upon addition of 32 μl of a 1·0 M succinate solution; (3) succinate ATP rate, upon addition of 20 μl of a 0·10 M ATP solution; and (4) succinate ADP rate, upon final addition of 10 μl of a 0·05 M ADP solution. From previous experiments in our laboratories, we found that the concentrations of succinate, ATP and ADP used here are able to provide full saturation of the reaction vessels and thus permit maximal stimulation of oxygen consumption of the particular parameters. Under normal conditions, exogenous succinate would give substantial stimulation; endogenous ATP would increase this stimulation slightly, concomitant with endogenous ATPase activity in the "tightly coupled" mitochondria; and exogenous ADP, being the rate-limiting factor, would give maximal stimulation of oxygen consumption.

Protein nitrogen determinations were done on 0·1-ml aliquots of each organ homogenate, using the micro-Kjeldahl technique reported by Ma and Zuazaga.[4]

TABLE 1. MEAN VALUES OF CONTROL ($\bar{X}_c$) AND DRUG-INJECTED ($\bar{X}_e$) RESPIRATORY RATES (IN μmoles O_2 scc per mg N) OF MOUSE BRAIN HOMOGENATES

Drug group*	Sacrifice time interval† (hr)	No. of mice	Endogenous rate		Succinate rate (after addition of 32 μl of a 1·00 M succinate solution)		Succinate–ATP rate (after addition of 20 μl of a 0·10 M ATP solution)		Succinate–ADP rate (after addition of 10 μl of a 0·05 M ADP solution)	
			$\bar{X}_c$	$\bar{X}_e$	$\bar{X}_c$	$\bar{X}_e$	$\bar{X}_c$	$\bar{X}_e$	$\bar{X}_c$	$\bar{X}_e$
PB	0·5	8	0·224	0·244	0·332	0·374	0·480	0·561	0·581	0·594
AS	0·5	8	0·277	0·228	0·569	0·432	0·612	0·503	0·627	0·496
THC	0·5	7	0·255	0·090	0·401	0·177	0·440	0·242	0·515	0·262
PB	1·5	8	0·105	0·170	0·170	0·269	0·302	0·455	0·342	0·455
AS	1·5	8	0·291	0·176	0·430	0·268	0·732	0·449	0·778	0·518
THC	1·5	7	0·264	0·125	0·462	0·181	0·537	0·268	0·498	0·346
PB	2·5	8	0·232	0·193	0·406	0·354	0·539	0·490	0·558	0·537
AS	2·5	8	0·303	0·181	0·459	0·376	0·732	0·531	0·812	0·597
THC	2·5	7	0·209	0·188	0·340	0·249	0·439	0·311	0·507	0·401
PB	8	8	0·109	0·127	0·220	0·247	0·325	0·401	0·307	0·415
AS	8	8	0·244	0·247	0·433	0·618	0·598	0·859	0·715	0·887
THC	8	7	0·177	0·159	0·289	0·253	0·340	0·335	0·373	0·379

* PB = pentobarbital sodium; AS = DL-amphetamine sulfate; THC = 1-Δ^9-tetrahydrocannabinol.

† The sacrifice time interval represents the elapsed time, in hr, between administration of the drug and sacrifice of the animal.

TABLE 2. MEAN VALUES OF CONTROL ($\bar{X}_c$) AND DRUG-INJECTED ($\bar{X}_e$) RESPIRATORY RATES (IN μmoles O_2/sec per mg N) OF MOUSE HEART HOMOGENATES

Drug group*	Sacrifice time interval† (hr)	No. of mice	Endogenous rate		Succinate rate (after addition of 32 μl of a 1·00 M succinate solution)		Succinate–ATP rate (after addition of 20 μl of a 0·10 M ATP solution)		Succinate–ADP rate (after addition of 10 μl of a 0·05 M ADP solution)	
			$\bar{X}_c$	$\bar{X}_e$	$\bar{X}_c$	$\bar{X}_e$	$\bar{X}_c$	$\bar{X}_e$	$\bar{X}_c$	$\bar{X}_e$
PB	0·5	8	0·253	0·336	0·932	1·002	0·988	1·019	0·981	1·053
AS	0·5	8	0·180	0·131	1·648	1·564	1·637	1·480	1·590	1·480
THC	0·5	7	0·407	0·206	0·573	0·443	0·639	0·469	0·742	0·484
PB	1·5	8	0·213	0·184	0·718	0·799	0·792	0·720	0·672	0·773
AS	1·5	8	0·197	0·135	0·993	0·935	0·857	0·799	0·876	0·833
THC	1·5	7	0·451	0·372	1·030	0·691	0·595	0·492	0·648	0·595
PB	2·5	8	0·246	0·264	0·768	0·793	0·799	0·767	0·761	0·735
AS	2·5	8	0·203	0·121	0·982	0·758	1·091	0·761	1·017	0·744
THC	2·5	7	0·532	0·520	1·647	1·375	0·593	0·526	0·617	0·486
PB	8	8	0·166	0·172	0·508	0·534	0·505	0·627	0·475	0·623
AS	8	8	0·174	0·145	0·939	1·127	1·038	1·139	1·029	1·151
THC	8	7	0·648	0·727	2·240	2·434	1·188	1·344	1·383	1·421

* PB = pentobarbital sodium; AS = DL-amphetamine sulfate; THC = 1-Δ^9-tetrahydrocannabinol.

† The sacrifice time interval represents the elapsed time, in hr, between administration of the drug and sacrifice of the animal.

TABLE 3. DIFFERENCES IN RESPIRATORY RATES (IN μmoles O_2 sec·mg N) OF MOUSE BRAIN HOMOGENATES FROM DRUG-TESTED ANIMALS AND CONTROLS*

Drug group†	Sacrifice time interval‡ (hr)	No. of mice	Endogenous rate	Succinate rate (after addition of 32 μl of a 1·00 M succinate solution)	Succinate–ATP rate (after addition of 20 μl of a 0·10 M ATP solution)	Succinate–ADP rate (after addition of 10 μl of a 0·05 M ADP solution)
PB	0·5	8	−0·020 ± 0·088	−0·042 ± 0·204	−0·081 ± 0·130	−0·013 ± 0·144
AS	0·5	8	0·049 ± 0·038§	0·137 ± 0·078§	0·109 ± 0·091§	0·131 ± 0·117§
THC	0·5	7	0·165 ± 0·044§	0·224 ± 0·060§	0·198 ± 0·145§	0·253 ± 0·098§
PB	1·5	8	−0·065 ± 0·077	−0·099 ± 0·113	−0·153 ± 0·222	−0·113 ± 0·154
AS	1·5	8	0·115 ± 0·054§	0·162 ± 0·057§	0·283 ± 0·123§	0·260 ± 0·170§
THC	1·5	7	0·139 ± 0·026§	0·281 ± 0·090§	0·269 ± 0·105§	0·152 ± 0·043§
PB	2·5	8	0·039 ± 0·034§	0·052 ± 0·080	0·049 ± 0·219	0·021 ± 0·156
AS	2·5	8	0·122 ± 0·021§	0·083 ± 0·103	0·201 ± 0·130§	0·215 ± 0·126§
THC	2·5	7	0·021 ± 0·019§	0·091 ± 0·038§	0·128 ± 0·035§	0·106 ± 0·090§
PB	8	8	−0·018 ± 0·021	−0·027 ± 0·036	−0·076 ± 0·067§	−0·108 ± 0·122
AS	8	8	−0·003 ± 0·030	−0·185 ± 0·118§	−0·261 ± 0·117§	−0·172 ± 0·128§
THC	8	7	0·018 ± 0·030	0·036 ± 0·054	0·005 ± 0·108	−0·006 ± 0·072

* Each rate represents the difference between the mean values of a drug-injected group and its control group $\pm t_{0.025,\nu}$ S.E. In this particular case, two-sided confidence intervals were calculated at the 0·95 probability level; therefore, 2α equals 0·05, or α equals 0·025. Moreover, $\nu = (N_1 + N_2 - 2) = 12$ or 14, depending upon the above drug used.

† PB = pentobarbital sodium; AS = DL-amphetamine sulfate; THC = 1-Δ^9-tetrahydrocannabinol.

‡ The sacrifice time interval I represents the elapsed time, in hr, between administration of the drug and sacrifice of the animal.

§ Significant ($P < 0·05$) difference between mean respiratory rates obtained in the homogenates of drug-tested animals and homogenates of their control animals. Mean values for control animals were set at 0·000 for statistical evaluations.

TABLE 4. DIFFERENCES IN RESPIRATORY RATES (IN μmoles O_2/sec/mg N) OF MOUSE HEART HOMOGENATES FROM DRUG-TESTED ANIMALS AND CONTROLS*

Drug group†	Sacrificial time interval ‡	No. of mice	Endogenous rate	Succinate rate (after addition of 32 μl of a 1·00 M succinate solution)	Succinate ATP rate (after addition of 20 μl of a 0·10 M ATP solution)	Succinate–ADP rate (after addition of 10 μl
PB	0·5	8	−0·083 ± 0·085	−0·070 ± 0·092	−0·031 ± 0·102	−0·072 ± 0·165
AS	0·5	8	0·049 ± 0·028§	0·084 ± 0·075§	0·157 ± 0·041§	0·110 ± 0·057§
THC	0·5	7	0·201 ± 0·046§	0·130 ± 0·062§	0·170 ± 0·050§	0·258 ± 0·042§
PB	1·5	8	0·029 ± 0·041	−0·081 ± 0·157	0·072 ± 0·095	−0·101 ± 0·064§
AS	1·5	8	0·062 ± 0·032§	0·058 ± 0·088	0·058 ± 0·072	0·043 ± 0·058
THC	1·5	7	0·079 ± 0·048§	0·339 ± 0·161§	0·103 ± 0·044	0·053 ± 0·061
PB	2·5	8	−0·018 ± 0·037	−0·025 ± 0·165	0·032 ± 0·125	0·026 ± 0·085
AS	2·5	8	0·082 ± 0·037§	0·224 ± 0·118§	0·330 ± 0·142§	0·273 ± 0·093§
THC	2·5	7	0·012 ± 0·073	0·272 ± 0·135§	0·067 ± 0·082§	0·131 ± 0·081§
PB	8	8	−0·006 ± 0·032	−0·026 ± 0·062	−0·122 ± 0·131	−0·148 ± 0·083§
AS	8	8	0·029 ± 0·025§	−0·118 ± 0·110§	−0·101 ± 0·145	0·122 ± 0·078§
THC	8	7	−0·079 ± 0·062§	−0·194 ± 0·094§	0·046 ± 0·085§	−0·038 ± 0·073

* Each rate represents the difference between the mean values of a drug-injected group and its control group $\pm t_{0.025,\nu}$ S.E. In this particular case, two-sided confidence intervals were calculated at the 0·95 probability level; therefore, 2α equals 0·05, or α equals 0·025. Moreover, $\nu = (N_1 + N_2 - 2) = 12$ or 14, depending upon the above drug used.

† PB = pentobarbital sodium; AS = DL-amphetamine sulfate; THC = 1-Δ^9-tetrahydrocannabinol.

‡ The sacrifice time interval represents the elapsed time, in hr, between administration of the drug and sacrifice of the animal.

§ Significant ($P < 0·05$) difference between mean respiratory rates obtained in the homogenates of drug tested animals and homogenates of their control animals. Mean values for control animals were set at 0·000 for statistical evaluations.

Therefore, oxygen consumption rates were standardized and expressed as μmoles oxygen consumed/sec per mg of nitrogen.

The data are represented: (1) as absolute mean values (Tables 1 and 2), and (2) statistically as the difference in average oxygen consumption rates between the experimental and the control mice (Tables 3 and 4). Thus, for a particular organ, parameter of respiration, and sacrifice time interval, three contrasting levels of oxygen consumption were computed, each level representing one of the three test-drug/saline-control situations. Incorporating a Student's analysis with pooled variance, confidence intervals at a 95 per cent level were calculated for each computed level. Moreover, if the confidence interval includes the zero (0·000) baseline, then the difference between the average experimental and control values may not be significantly different (that is, stimulation or depression) from zero.

RESULTS

Tables 1 and 2 represent mean values of oxygen consumption by brain and heart homogenates, respectively, from control and drug-injected mice. However, statistical analysis, enabling interpretation of the data, is represented in Tables 3 and 4.

Table 3 compares differences in the respiratory rates of the brain homogenates. Generally, pentobarbital had little significant effect on brain respiration at any of the four time intervals. In contrast, both DL-amphetamine and Δ^9-THC significantly stimulated respiration for at least the first 2·5 hr after injection. However, after 8 hr, mice injected with DL-amphetamine showed significantly depressed brain respiration, while brain respiration of mice treated with Δ^9-THC was not significantly affected.

Table 4 compared differences in the respiratory rates of the heart homogenates. Again, pentobarbital generally had little significant effect on cardiac tissue respiration at any of the four time intervals. DL-Amphetamine produced uniformly significant stimulation of respiration after 0·5 and 2·5 hr, while only elevating endogenous levels at 1·5 and 8 hr; however, it also caused a significant depression of respiration after 8 hr. Significant elevation of oxygen consumption following Δ^9-THC administration was generally seen after 0·5, 1·5 and 2·5 hr, with significant depression after 8 hr.

DISCUSSION

Both brain and heart respiration appeared to be little affected by the pentobarbital. DL-Amphetamine stimulated respiration in both heart and brain significantly after 0·5, 1·5 and 2·5 hr. After 8 hr, both significant depression and stimulation were seen in cardiac respiration, while brain respiration was only depressed. Δ^9-THC administration, like DL-amphetamine, caused significant stimulation of respiration in both brain and heart at 0·5, 1·5 and 2·5 hr. However, after 8 hr, brain respiration showed no significant effect from the Δ^9-THC, while heart respiration was significantly depressed.

Investigations with pentobarbital and related barbiturates have shown that these compounds are intracellular depressants of tissue oxygen consumption. Although much work has produced different theories of mechanism, it is agreed that many barbiturates, including pentobarbital, can depress cerebral[5–8] and cardiac[9–12] oxygen consumption. However, the lack of expected significant change in our measured oxygen consumption rates after pentobarbital administration was probably due to

the following possibility: the dose was, in itself, pharmacologically active, but due to the inability of cardiac tissue to concentrate pentobarbital,[13] strongly coupled with a probable dilution to low tissue levels of the bound drug during preparation of the homogenates, the drug's effects were too greatly weakened to be measured.

The dichotomy of effects in the brain that we noted with DL-amphetamine is paradoxical, but supporting evidence has been reported for both effects. The significant increase in oxygen consumption we noted for the first 2·5 hr appears to substantiate findings by Edel[14] and by Lewis and Van Petten,[15] implicating DL-amphetamine's central nervous system hyperactivity with increased turnover of brain nucleotide (ATP and creatine phosphate) levels. Concerning the depressed oxygen consumption, Mann and Quastel[16] noted that at time intervals far shorter than 8 hr, amphetamine (Benzedrine) at relatively high concentrations inhibited oxygen consumption *in vitro* by cerebral cortex slices, while low concentrations produced no effective change. However, their theory of amphetamine acting as a direct monoamine oxidase (MAO) inhibitor has been disclaimed in other work.[17–19]

In the heart, as well as in the brain, it appears that increased oxygen consumption, associated with increased oxidative phosphorylation and nucleotide turnover,[20, 21] provides a direct means for producing the high energy compounds utilized in amphetamine-induced hyperactivity. Our measured decline of oxygen consumption through at least 1·5 hr is in accord with the findings of Fuller and Hines.[22] They observed the ability of the mouse heart to bind or concentrate D-amphetamine, or to do both, relative to the plasma concentration, at a dosage comparable to ours (10 mg/kg), after 1 hr. Moreover, after injection of a low dose, they found that D-amphetamine levels in the heart, as well as in other organs, declined logarithmically through time, starting from the first hr. However, the restimulation at 2·5 hr is then questionable and might indicate the concurrent release of a large quantity of amphetamine from certain tissue stores. The depression at 8 hr is intriguing, in that the endogenous rate is slightly stimulated; yet, the parameter which represents the possibility for maximal stimulation (succinate–ADP rate) is here significantly depressed, a phenomenon which happened concurrently in the brain.

The findings of increased oxygen consumption at all parameters by the brain, for at least the first 2·5 hr after injection of Δ^9-THC, are substantiated by previous work with mice in our laboratories. Harclerode and King (unpublished data) found that *Cannabis* red oil extract, in a dose containing 50 mg/kg of Δ^9-THC, significantly stimulated endogenous and succinate–ADP rates in the brain and liver after 2 hr ($P < 0{\cdot}05$) and in the brain after 6 hr ($P < 0{\cdot}01$). In dosage response studies with synthetic Δ^9-THC, Harclerode *et al.* (unpublished data) observed significantly stimulated endogenous and succinate–ADP rates in the brain after 1 hr, at doses of 10, 25 and 50 mg/kg ($P < 0{\cdot}05$).

It is possible that there exist correlations between the effect of Δ^9-THC on oxygen consumption and its neurochemical behavior. Within our measured time periods of stimulated oxygen consumption, and using low doses of Δ^9-THC, Holtzman *et al.*[23] and Schildkraut and Efron[24] noted increases (not significant in the latter study) in endogenous serotonin levels and decreases in endogenous norepinephrine levels in the rat brain; however, at high doses, Holtzmann *et al.*[23] found increased endogenous norepinephrine levels. Moreover, Constantinidis and Miras[25] noted increased norepinephrine levels in the rat hypothalamus after Δ^9-THC administration. These

findings suggest enhancement of re-uptake of increased synthesis of the norepinephrine; however, whether the energy requirements for these mechanisms necessitate significantly measurable increases in cerebral oxygen consumption cannot be conclusively stated.

Our dual findings of stimulation and depression of cardiac oxygen consumption have correlates in other previous research. Clinical studies have shown that marihuana ingestion in man produces, among other effects, tachycardia.[26] However, Δ^9-THC dose-dependent bradycardia in animals has been reported.[27,28] Our results give no concrete indication of mechanism, either directly on the cardiac tissue or through centrally mediated autonomic responses, by which Δ^9-THC mediates its effects on the heart. Through related experiments, for example, Oskoui[29] and Cavero and Jandhyala[27] attribute the observed bradycardia to a possible combination of both these mechanisms.

In retrospect, it is interesting to note that amphetamine also causes decreased norepinephrine levels and increased serotonin levels in the mouse brain, but unlike Δ^9-THC, amphetamine increases spontaneous motor activity and has been reported to cause increased cerebral norepinephrine levels,[30] while others[31] have noted increased serotonin levels or unchanged serotonin levels.[32] Finally, the precise mechanism whereby Δ^9-THC acts synergistically to prolong amphetamine hyperactivity and barbiturate sleeping time[33] is unknown. This might reflect the inhibition of the metabolism of both drugs by Δ^9-THC or an effect on neuronal (synaptic) membrane permeability, facilitating passage of these drugs. A possible direct effect by Δ^9-THC on mitochondrial function could be considered;[34,25] moreover, this effect could be dosage dependent.[36]

The differences shown in this study are probably not due to different degrees of aging between the three drug preparations and the control group, as determined by previous work with identical preparations both in our laboratories and in findings reported by Ziegler *et al.*[3] We did not determine at this time what, if any, effects the three drugs had *in vivo* on the degree of coupling of the mitochondria in the homogenates. Other investigators have pursued these effects *in vitro*.[5,7,36] It is very conceivable that any or all of these drugs could affect cerebral or cardiac metabolic rates, or both, *in vivo*, thus leading to differences: (1) in the rates of aging in the organs and in the various homogenates; and (2) in the degree of coupling during tests *in vitro*. Findings by Boime *et al.*[37] give importance to such considerations of aging on mitochondrial coupling. We therefore feel that this possibility should be pursued in further investigations with the drugs used in our work.

We also suggest that further studies include the addition *in vitro* of the active 11-hydroxy metabolite of Δ^8- or Δ^9-THC,[2,38] as well as administration of Δ^8-/Δ^9-THC *in vivo*. The 11-hydroxy metabolite is probably the means by which Δ^8- or Δ^9-THC exerts the eventual effects of marihuana in the various organs. However, administration of just Δ^8- or Δ^9-THC allows for the necessary biotransformation of THC isomers in the liver to the active form, with subsequent uptake[2,39] and binding within tissues.

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