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THE EFFECT OF Δ^9-TETRAHYDROCANNABINOL ON BODY TEMPERATURE AND BRAIN AMINE CONCENTRATIONS IN THE RAT AT DIFFERENT AMBIENT TEMPERATURES

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1 Rats were injected intravenously with 2 mg/kg (−)-*trans*-Δ^9-tetrahydrocannabinol (Δ^9-THC) at ambient temperatures of 4°, 21°, 31° and 37°C.

2 The general behaviour exhibited by rats treated with Δ^9-THC was similar at all four ambient temperatures.

3 Body temperatures were recorded continuously before and after drug administration. At 4° and 21°C, Δ^9-THC caused hypothermia whereas no change in body temperature occurred at 31° and 37°C.

4 The concentrations in the whole brain of noradrenaline (NA), dopamine, 5-hydroxytryptamine (5-HT) and 5-hydroxyindoleacetic acid (5-HIAA) were determined spectrophotofluorimetrically 1 h after drug administration. At 4°C Δ^9-THC caused an increase of 5-HT, at 21°C an increase of 5-HIAA, at 31°C an increase of 5-HIAA and a decrease of NA, and at 37°C an increase of 5-HT and 5-HIAA.

5 At all ambient temperatures, Δ^9-THC increased the brain levels of 5-HT and/or 5-HIAA. A correlation between the Δ^9-THC-induced hypothermic response and the possible alteration of brain 5-HT metabolism cannot be excluded.

Introduction

It is well documented that the administration of (−)-*trans*-Δ^9-tetrahydrocannabinol (Δ^9-THC) to laboratory animals results in hypothermia (Holtzman, Lovell, Jaffe & Freedman, 1969; Lomax, 1971; Sofia, 1972). The investigations of Feldberg & Myers (1963; 1964; 1965) provide the basis for the hypothesis that catecholamines and 5-hydroxytryptamine (5-HT) are involved in the central mechanism of temperature control. Holtzman *et al.* (1969) suggested that the hypothermic response in mice induced by Δ^9-THC is correlated to changes in the brain levels of noradrenaline (NA) and 5-HT. Other workers have found that Δ^9-THC or cannabis extracts cause brain NA concentrations to fall (Schildkraut & Efron, 1971), to rise (Constantinidis & Miras, 1971) or to remain unchanged (Maître, Staehelin & Bein, 1970; Mazurkiewicz-Kwilecki & Filczewski, 1973), whereas concentrations of 5-HT have been reported to increase (Schildkraut & Efron, 1971; Sofia, Dixit & Barry, 1971) or to remain unchanged (Gallager, Sanders-Bush & Sulser, 1972; Yagiela, McCarthy & Gibb, 1974).

In the light of these conflicting reports, it was decided to investigate the effect of Δ^9-THC on the body temperature of rats maintained at different ambient temperatures, and at the same time to examine whether a correlation exists between changes in body temperature and changes in brain monoamine concentrations. At different ambient temperatures, the Δ^9-THC-induced hypothermic response is modified (Haavik & Hardman, 1973) as is the dynamic state of brain monoamines (Reid, Volicer, Smookler, Beaven & Brodie, 1968).

Methods

Animals

Male albino Wistar rats weighing between 200 and 300 g were housed in an animal room at an ambient temperature of 21 ± 2°C and a 12 h light-dark cycle. Food and water were available *ad libitum*. For intravenous injection, a permanent polyethylene (PE 10) catheter was inserted into the external jugular vein under amylobarbitone sodium plus methohexitone sodium (i.p.) anaesthesia. Before surgery, animals were housed in group cages, but for the 48 h recovery period and during the experimental period, they were kept in individual cages. Rats were used either for

body temperature studies or brain amine determinations. All experiments were completed before midday.

Studies at different ambient temperatures

Four ambient temperatures were used in these studies, namely $4 \pm 1°$, $21 \pm 2°$, $31 \pm 1°$ and 37° to 39°C. At temperatures other than 21°C the animals were allowed a 3 h acclimatization period before the injection of Δ^9-THC or its vehicle.

Preparation of Δ^9-THC

A dispersion of Δ^9-THC in saline (0.9% w/v NaCl solution) using polyvinylpyrrolidone (PVP) following the method of Fenimore & Loy (1971) was used. Δ^9-THC (2 mg/kg) or PVP (40 mg/kg) was injected intravenously in a volume of 1 ml/kg body weight.

Body temperature studies

The body temperature of individually caged, unrestrained rats was recorded continuously for 3 h by means of a thermistor probe inserted 60–70 mm into the rectum 1 h before the administration of Δ^9-THC or PVP. Three thin pieces of adhesive tape held the probe in position relative to the tail. Temperatures were recorded continuously with either an Offner type R or a Riken Denshi pen recorder.

Brain amine determinations

One hour after the intravenous injection of Δ^9-THC 2 mg/kg or PVP 40 mg/kg, rats were killed by decapitation. Their brains were rapidly removed, blotted free from blood, frozen in liquid N_2 and stored at −20°C. For amine determinations, the frozen brains were weighed and, after thawing in a solution of 0.4 M perchloric acid containing 0.2% disodium edetate, homogenized in a motor driven, all glass homogenizer. The amines dopamine, NA and 5-HT were extracted from the homogenate using BIO-REX 70 (BIO-RAD Laboratories) according to the column procedure of Barchas, Erdelyi & Angwin (1972). 5-Hydroxyindoleacetic acid (5-HIAA) was further extracted from the first effluent off the column into *n*-butyl acetate made acidic by addition of 100 µl 3 M HCl. After removal of the aqueous phase, 5 ml 0.5 M phosphate buffer pH 7.0 was added to the organic phase and 5-HIAA was re-extracted into the buffered phase. The amines NA, dopamine and 5-HT were then eluted from the column with 5 ml 0.5 M acetic acid.

The extracted amines were then assayed spectrophotofluorimetrically as follows: dopamine, according to the method of Carlsson & Waldeck (1958); NA, according to the method of Weil-Malherbe (1971) and 5-HT and 5-HIAA according to the method of Lovenberg & Engelman (1971). The fluorescence developed was determined with an Aminco-Bowman spectrophotofluorimeter. The concentrations of brain amines are expressed in terms of the free base or acid.

Analysis of results

In the body temperature studies, results are expressed in 'Thermic Index' values as defined by Jori, Paglialunga & Garattini (1967). The Thermic Index is a measurement of the cumulative change in body temperature from the original which is calculated 5, 10, 15, 30, 45, 60, 75, 90, 105 and 120 min after the injection of Δ^9-THC or its vehicle. For testing the statistical significance of differences between means, Student's *t*-test was used (with the aid of a Cyber 74 computer).

Drugs

The following drugs and chemicals were used: amylobarbitone sodium (Amytal, Eli Lilly); dopamine hydrochloride (3-hydroxytyramine, Sigma); 5-hydroxyindoleacetic acid cyclohexyl ammonium salt (Sigma); 5-hydroxytryptamine creatinine sulphate (Koch-Light); methohexitone sodium (Brietal Sodium, Eli Lilly); (−)-noradrenaline hydrochloride (Levarterenol, Sigma); polyvinylpyrrolidone (Kollidon 25, BASF); (−)-*trans*-Δ^9-THC (Batch SSC 75814, NIMH). All reagents used for extraction and assay were of analytical grade.

Results

General behaviour

The behaviour of the rats was observed for a 2 h period following the intravenous injection of Δ^9-THC 2 mg/kg. After about 3 min the animals started an exploratory type of behaviour manifested as periodic walking around the cage and digging in the sawdust with their noses. This was accompanied by spontaneous jumping or 'jumping fits'. This period of abnormal motor activity, which lasted for about 20 min, appeared to be superimposed on a state of depression which became evident 10 min after the injection of Δ^9-THC. The depression was manifested as catatonia, depressed respiration and splayed rear legs. There appeared to be a decreased threshold to tactile stimuli because the rats squealed when held or touched. Catatonia lasted for about 1 hour. For the following hour general sedation prevailed. This type of behaviour occurred at each of the four ambient temperatures.

Table 1 Effect of four different ambient temperatures on the body temperatures of individually caged, untreated rats

Ambient temperature (°C)	*Body temperature* (°C ± s.e. mean)*	*Level of significance‡ (P value)* 4°C	21°C	31°C	37°C	*Body weight† (g ± s.e. mean)*
4	37.42 ± 0.19	—	0.212	0.002	0.000	256.5 ± 8.1 (15)
21	37.72 ± 0.15	0.212	—	0.008	0.000	260.4 ± 5.5 (21)
31	38.49 ± 0.23	0.002	0.008	—	0.001	255.8 ± 9.1 (11)
37	39.56 ± 0.17	0.000	0.000	< 0.001	—	246.9 ± 7.9 (15)

The figures in parentheses are the number of rats in each group. † The mean body weights of each group were not significantly different from each other.
* Body temperatures were recorded at 3 h after rats were placed in the different ambient temperature environments.
‡ *P* values were calculated by comparison of the body temperatures of the groups of rats at the different ambient temperatures.

Table 2 Effect of intravenous injections of Δ⁹-tetrahydrocannabinol (Δ⁹-THC) 2 mg/kg and polyvinylpyrrolidone (PVP) 40 mg/kg on the Thermic Index values of individually caged rats at different ambient temperatures

Ambient temperature (°C)	*Thermic Index ± s.e. mean* PVP	Δ⁹-THC	*Body weight† ± s.e. mean* PVP	Δ⁹-THC
4	+0.96 ± 2.22 (6)	−15.41 ± 1.86 (9)*	260.3 ± 14.2 (6)	254.0 ± 10.3 (9)
21	−1.80 ± 0.94 (10)	−11.66 ± 1.65 (11)*	259.0 ± 9.9 (10)	261.6 ± 5.8 (11)
31	+0.17 ± 2.83 (5)	−2.97 ± 2.11 (6)	256.2 ± 14.3 (5)	255.5 ± 13.1 (6)
37	−0.20 ± 0.58 (6)	+1.49 ± 0.54 (9)	254.7 ± 12.7 (6)	247.8 ± 10.6 (9)

Rats were injected either with Δ⁹-THC or PVP 3 h after being placed in a specific ambient temperature where they remained for at least a further 2 hours. Figures in parentheses indicate the number of animals in each group. † The mean body weights were not significantly different from each other.
The Thermic Index is a measurement of the cumulative change in body temperature from the original calculated at 5, 10, 15, 30, 45, 60, 75, 90, 105 and 120 min after drug administration.
* $P < 0.001$, compared with PVP.

Table 3 Mean body weight of rats receiving either polyvinylpyrrolidone (PVP) 40 mg/kg or Δ⁹-tetrahydrocannabinol (Δ⁹-THC) 2 mg/kg

Ambient temperature (°C)	*Body weight (g ± s.e. mean)** PVP	Δ⁹-THC
4	259.0 ± 6.3 (24)	253.2 ± 4.1 (47)
21	250.9 ± 6.6 (18)	255.9 ± 4.8 (36)
31	254.5 ± 8.2 (12)	260.3 ± 5.4 (24)
37	250.5 ± 7.6 (13)	248.8 ± 5.2 (23)

Brains from these animals were used in the determination of brain amine concentrations at different ambient temperatures. Figures in parentheses indicate the number of rats in each group. * The mean body weights of each group were not significantly different from each other.

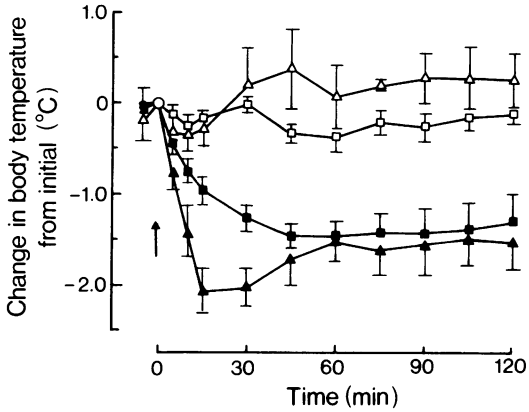

Figure 1 Effect of Δ^9-tetrahydrocannabinol (Δ^9-THC) 2 mg/kg injected intravenously, on the body temperature of rats kept at ambient temperatures of 4° (▲) and 21°C (■). For comparison, the effect of an injection of polyvinylpyrrolidone (PVP, 40 mg/kg) on the body temperature of rats kept at 4° (△) and 21°C (□) is also shown. Each point is the mean of results from at least 6 rats. Vertical lines show s.e. means. The body temperatures were recorded for 1 h before, and 2 h after the injections at time 0 as indicated by the arrow.

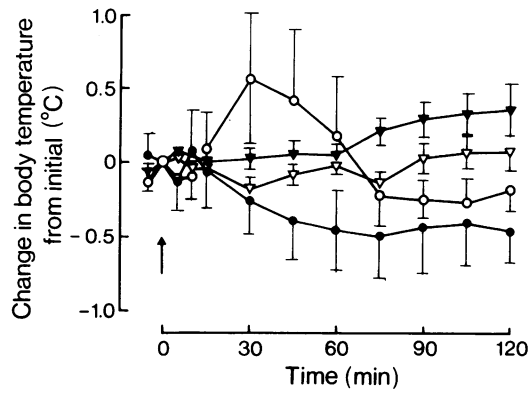

Figure 2 Effect of Δ^9-tetrahydrocannabinol (Δ^9-THC) 2 mg/kg, injected intravenously, on the body temperature of rats kept at ambient temperatures of 31° (●) and 37°C (▼). For comparison the effect of an injection of polyvinylpyrrolidone (PVP, 40 mg/kg) on the body temperature of rats kept at 31° (○) and 37°C (▽) is also shown. Each point is the mean of results from at least 5 rats. Vertical lines show s.e. means. The body temperatures were recorded for 1 h before, and 2 h after the injections at time 0 as indicated by the arrow.

Effect of different ambient temperatures on the body temperature of untreated rats

Table 1 shows the mean body temperatures of untreated rats as recorded 3 h after the animals were placed at ambient temperatures of 4°, 21°, 31° or 37°C. The continuous recording of the rectal temperature was started 2 h after introducing the rats to the various ambient temperatures. The body temperatures of rats at 37°C were significantly higher than those of rats at 4°, 21° and 31°C ($P < 0.001$). Rats kept at 31°C had a significantly higher body temperature than those kept at 4° and 21°C ($P < 0.01$). There was no significant difference between the body temperatures of rats at 4° and 21°C.

The mean body weights of rats in each group in all experiments have been included in Tables 1–3 to show that, although animals having a large weight range were used, there was no significant difference in the mean body weights between the groups.

Effect of ambient temperature on the body temperature of rats injected with Δ^9-THC

The temperature of rats injected with Δ^9-THC 2 mg/kg and kept at ambient temperatures of 4° and 21°C was monitored for 2 h following the injection (see Figure 1). At both ambient temperatures Δ^9-THC significantly decreased body temperature compared to PVP-treated controls. At 21°C the maximum change in body temperature was reached approximately 1 h after administration, at 4°C the maximum hypothermic effect (−2.1°C) occurred 15 min after the administration of Δ^9-THC. At both ambient temperatures, 6 to 8 h elapsed before body temperature returned to pre-injection values.

Figure 2 shows the body temperature of rats kept at 31° and 37°C during the 2 h period following administration of Δ^9-THC 2 mg/kg. At these elevated ambient temperatures Δ^9-THC did not decrease the body temperatures when compared with those of PVP-treated controls. At 37°C there even occurred a significant increase ($P < 0.02$) 75 min after the injection of Δ^9-THC.

To enable a statistical comparison of the effects of Δ^9-THC 2 mg/kg and PVP 40 mg/kg on the body temperature of rats placed at the four ambient temperatures, the Thermic Index values were calculated from the temperature measured at 5, 10, 15, 30, 45, 60, 75, 90, 105 and 120 min following drug administration (see Table 2). At the four ambient temperatures the Thermic Index values of rats treated with PVP were not significantly different from one another. The Thermic Index values of rats treated with Δ^9-THC at 4° and 21°C were not significantly different from one another; however, as the ambient temperature was increased from 21° to 31°C and from 31° to 37°C, the Thermic Index values of rats

treated with Δ^9-THC increased significantly ($P < 0.05$). The Thermic Index values obtained from rats treated with Δ^9-THC compared to those of PVP-treated rats were significantly lower at 4° and 21°C ($P < 0.001$), whereas at 31° and 37°C there was no significant difference between the two treatments.

Effect of ambient temperature and Δ^9-THC on the concentration of amines in whole brain

The NA and dopamine concentrations in whole brain are tabulated in Table 4. No significant differences occurred between the concentrations of NA in the brains of PVP-treated rats at each of the four ambient temperatures. There was a small reduction (−9%) in brain dopamine in PVP-treated animals at 31°C when compared to that at 21°C ($P < 0.05$). At the four ambient temperatures, Δ^9-THC did not alter the brain concentrations of NA and dopamine, except for a small (−8%) but statistically significant ($P < 0.02$) decrease in the NA concentration at 31°C.

The concentrations of 5-HT and 5-HIAA in the whole brain are shown in Table 5. The 5-HT concentration in PVP-treated rats kept at 37°C was significantly greater (+9% and +11%) than that of PVP-treated animals at 4° and 21°C ($P < 0.05$). The 5-HIAA concentration in PVP-treated rats kept at 37°C was also significantly higher (+35%, 38% and 15%) than that of PVP-treated rats kept at 4°, 21° and 31°C ($P < 0.02$). These values obtained at 31°C were also significantly higher (+20%, +18%) than those at 4° and 21°C ($P < 0.001$). Administration of Δ^9-THC caused a significant increase in the brain content of 5-HT by 16% and 10% in rats kept at 4° and 37°C when compared with that of PVP-treated control animals kept at the same temperatures ($P < 0.01$). At an ambient temperature of 21°C, Δ^9-THC increased the brain content of 5-HIAA by 32% relative to PVP-treated rats ($P < 0.0001$). In rats kept at 31°C, there was also an increase in the brain content of 5-HIAA (+18%, $P < 0.005$) compared to that of PVP-treated controls. In the rats kept at 37°C, the increase amounted to +15% ($P < 0.05$).

Discussion

At ambient temperatures of 4°, 21°, 31° and 37°C the general behaviour of rats following the intravenous administration of Δ^9-THC 2 mg/kg in this

Table 4 Concentrations of noradrenaline and dopamine in whole brain samples of rats 1 h after intravenous injection of Δ^9-tetrahydrocannabinol (Δ^9-THC) 2 mg/kg or polyvinylpyrrolidone (PVP) 40 mg/kg at different ambient temperatures

Ambient temperature (°C)	*Noradrenaline (μg/g ± s.e. mean)*		*Dopamine (μg/g ± s.e. mean)*	
	PVP	*Δ^9-THC*	*PVP*	*Δ^9-THC*
4	0.413 ± 0.028 (22)	0.457 ± 0.020 (42)	0.910 ± 0.027 (23)	0.958 ± 0.022 (47)
21	0.434 ± 0.024 (18)	0.422 ± 0.022 (35)	0.911 ± 0.023 (18)	0.928 ± 0.022 (36)
31	0.446 ± 0.008 (12)	0.408 ± 0.006 (24)*	0.831 ± 0.026 (12)	0.814 ± 0.029 (24)
37	0.462 ± 0.012 (13)	0.460 ± 0.005 (23)	0.858 ± 0.028 (13)	0.838 ± 0.025 (23)

Figures in parentheses indicate the number of animals in each group. Significance of difference from corresponding PVP controls: * $P < 0.002$.

Table 5 Concentrations of 5-hydroxytryptamine (5-HT) and 5-hydroxyindoleacetic acid (5-HIAA) in whole brain samples of rats 1 h after intravenous injection of Δ^9-tetrahydrocannabinol (Δ^9-THC) 2 mg/kg or polyvinylpyrrolidone (PVP) 40 mg/kg at different ambient temperatures

Ambient temperatures (°C)	*5-HT (μg/g ± s.e. mean)*		*5-HIAA (μg/g ± s.e. mean)*	
	PVP	*Δ^9-THC*	*PVP*	*Δ^9-THC*
4	0.452 ± 0.010 (22)	0.525 ± 0.013 (47)‡	0.907 ± 0.026 (24)	0.964 ± 0.034 (45)
21	0.443 ± 0.010 (16)	0.451 ± 0.009 (36)	0.890 ± 0.033 (12)	1.178 ± 0.034 (23)‡
31	0.477 ± 0.019 (12)	0.492 ± 0.020 (24)	1.070 ± 0.027 (11)	1.262 ± 0.034 (24)‡
37	0.491 ± 0.016 (13)	0.545 ± 0.011 (23)†	1.226 ± 0.046 (13)	1.418 ± 0.061 (23)*

Figures in parentheses indicate the number of animals in each group.
Significance of difference from corresponding PVP controls: * $P < 0.05$; † $P < 0.01$; ‡ $P < 0.002$.

study was qualitatively similar to that observed by Gallager *et al.* (1972) and Paton & Pertwee (1973). The jumping fits observed in about half the animals within the first 15 min after drug administration have also been reported by Schildkraut & Efron (1971) and Goldman, Dagirmanjian, Drew & Murphy (1975). The latter authors propose that this jumping behaviour may involve tryptaminergic mechanisms. Our results are in agreement with this suggestion since changes in the brain concentrations of 5-HT and/or 5-HIAA occurred at all four ambient temperatures. This study also confirms that, in laboratory animals, administration of Δ^9-THC causes a decrease in body temperature (Holtzman *et al.*, 1969; Lomax, 1971; Sofia, 1972). The magnitude of the hypothermic response to Δ^9-THC 2 mg/kg calculated as the Thermic Index, is dependent on ambient temperature. As the ambient temperature increases from 4° to 37°C there is a corresponding increase in the Thermic Index of Δ^9-THC treated rats; at ambient temperatures of 4° and 21°C, Δ^9-THC produces hypothermia, whereas at ambient temperatures of 31° and 37°C, no significant hypothermia is observed. These results are in agreement with those of Haavick & Hardman (1973) who observed a progressive decrease of the hypothermic response of mice to Δ^9-THC at ambient temperatures between 10°–35°C. The rate of change of body temperature after Δ^9-THC injection was also dependent on the ambient temperature. At an ambient temperature of 4°C the lowest values were already reached 15 min after the drug injection, at 21°C only after about 40 minutes. After 45 min there was no difference in the body temperatures of drug-treated animals kept at 4° or 21°C. The body temperatures of both groups of rats remained significantly lower than those of PVP-injected control animals kept at these ambient temperatures. These results indicate that in the rat Δ^9-THC produces hypothermia and not poikilothermia as has been observed in dogs after administration of the synthetic tetrahydrocannabinol derivative, dimethyl heptyl pyran (Hardman, Domino & Seevers, 1971).

The differences in body temperature of untreated rats observed 3 h after exposure to ambient temperatures of 4°, 21°, 31° or 37°C (see Table 1) are similar to those reported by Ingenito & Bonnycastle (1967) and Simmonds (1969). The hyperthermia seen in control rats at 31° and 37°C was not associated with alterations of the brain concentrations of NA or dopamine as has also been reported by Ingenito & Bonnycastle (1967) and Reid *et al.* (1968). Simmonds (1969) found that alterations of ambient temperature resulted in an increased turnover of NA, although the concentrations of NA in the hypothalamus remained unaltered. The control rats studied in the present experiments showed significantly higher brain concentrations of 5-HIAA when they were kept at 31° and 37°C than at 4° and 21°C. The brain concentrations of 5-HT in control rats only increased as the ambient temperature increased to 37°C. These results are in agreement with those of Reid *et al.* (1968) and Tagliamonte, Tagliamonte, Perez-Cruet, Stern & Gessa (1971) but differ from those of Ingenito & Bonnycastle (1967).

The effect of Δ^9-THC on rat brain monoamines appeared to be associated with changes in the brain content of 5-HT and 5-HIAA. When compared with PVP-treated rats, the Δ^9-THC treated rats showed at 4°C an increase in 5-HT, at 21°C an increase in 5-HIAA, at 31°C an increase in 5-HIAA (and a decrease in NA) and at 37°C an increase in both 5-HT and 5-HIAA. The small fall in the NA level at 31°C agrees with the observations of Holtzman *et al.* (1969) and Schildkraut & Efron (1971). The observation that Δ^9-THC did not alter the brain concentration of dopamine at any ambient temperature is consistent with the findings of Maître *et al.* (1970), who showed that, while rat brain NA and dopamine contents were unaffected by Δ^9-THC, there was an increase in brain catecholamine turnover.

In preliminary experiments with pargyline we observed that Δ^9-THC does not block acid transport from the central nervous system. Consequently, at ambient temperatures of 21°, 31° and 37°C, the rises in 5-HIAA concentrations may indicate an alteration in 5-HT metabolism. An increase in brain 5-HT content after Δ^9-THC was also reported by Sofia *et al.* (1971) but not by Gallager *et al.* (1972). Since changes in ambient temperature can alter monoamine metabolism (Reid *et al.*, 1968; Simmonds, 1969; 1970), it appears reasonable to suggest that Δ^9-THC has altered the 5-HT metabolism at all four ambient temperatures used.

In conclusion, the results of the present investigation demonstrate that the Δ^9-THC-induced hypothermia is dependent on ambient temperature. Although the apparent alteration in 5-HT metabolism at all ambient temperatures may not be linked with the hypothermic responses, such a correlation cannot be excluded.

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