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CHANGES IN BODY TEMPERATURE AND OXYGEN CONSUMPTION RATE OF CONSCIOUS MICE PRODUCED BY INTRAHYPOTHALAMIC AND INTRACEREBROVENTRICULAR INJECTIONS OF Δ^9-TETRAHYDROCANNABINOL

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1 Δ^9-Tetrahydrocannabinol (Δ^9-THC) was injected into the preoptic area of the anterior hypothalamus or into the third or fourth cerebral ventricle of the conscious mouse through a chronically implanted cannula and the effects on body temperature and oxygen consumption rate were measured.

2 At an ambient temperature of 22°C, injections of Δ^9-THC into the fourth ventricle (5 and 10 μg) produced dose-dependent falls in rectal temperature. Hypothermia was also observed after injections of the drug into the hypothalamus (5 and 10 μg) or into the third ventricle (10 μg).

3 The hypothermia produced by Δ^9-THC was associated with a fall in oxygen consumption rate. Falls in rectal temperature and in oxygen consumption rate were significantly greater after injection of Δ^9-THC than after injection of the drug vehicle, Tween 80.

4 The falls in rectal temperature and oxygen consumption rate produced by injection of Δ^9-THC into the fourth ventricle were abolished by elevation of the ambient temperature from 22 to 32°C.

5 A pretreatment that consisted of subcutaneous injections of Δ^9-THC (20 mg/kg) given once daily for three days produced tolerance to the hypothermic effect of the drug when injected on day 4 either into the fourth ventricle (10 μg) or into a lateral tail vein (2.0 mg/kg).

6 The results suggest that Δ^9-THC acts centrally to alter thermoregulation in mice not only when it is injected directly into the hypothalamus or cerebral ventricles but also when it is given intravenously. After intraventricular or intravenous administration the drug may act at extrahypothalamic as well as at hypothalamic sites. The data also support the hypothesis that in mice, tolerance to the hypothermic effect of Δ^9-THC is pharmacodynamic and does not depend on changes in metabolism or distribution of the drug.

Introduction

Little is yet known about the mechanisms responsible for the pharmacological effects of cannabis or of its main centrally active constituent Δ^9-tetrahydrocannabinol (Δ^9-THC). One of the characteristic pharmacological properties of these substances is the ability to lower body temperature (see Paton & Pertwee, 1973; Haavik & Hardman, 1979). The thermoregulatory system could provide a particularly useful model with which to investigate the mechanisms of action of cannabinoids in the whole animal since drug-induced changes in thermoregulation can be studied in unanaesthetized animals and since the physiological basis of thermoregulation is relatively well understood. In the present study a search was made for the sites at which Δ^9-THC acts to alter thermoregulation. Since there was already some evidence that at least some of these sites are located in the brain (Gill, Paton & Pertwee, 1970; Haavik, Collins & Hardman, 1975; Schmeling & Hosko, 1980), Δ^9-THC was injected into the preoptic area of the anterior hypothalamus and into the third and fourth cerebral ventricles. Mice were used because this species is particularly sensitive to the hypothermic effect of the drug. Both deep body temperature and oxygen consumption rate were monitored since, in the mouse at least, the hypothermic effect of Δ^9-THC is thought to be due largely to an effect on heat production (Pertwee & Tavendale, 1977).

Some of the results described in this paper were presented to the British Pharmacological Society (Fitton & Pertwee, 1981).

Methods

Adult 20 to 28 g male albino mice (MF1 strain) were used. Intrahypothalamic injections were made unilaterally into the preoptic area of the anterior

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hypothalamus (Nyemitei-Addo & Pertwee, 1981) and intraventricular injections into the third or fourth ventricles of the brain. For injection into the third ventricle a cannula guide (Nyemitei-Addo, Pertwee & Tavendale, 1980) was implanted chronically to a depth of 4.5 mm, 2.8 mm rostal to the lambda. For injection into the fourth ventricle, the cannula guide was implanted to a depth of 3 mm, 1.8 mm caudal to the lambda. Injections (0.5 μl) were made over a period of 1 min through an injection cannula, the tip of which extended 1 mm beyond that of the guide. The microinjection system and all glassware and saline used were sterile and pyrogen-free as described by Dascombe & Milton (1975). Each experiment was concluded by injecting methylene blue through the injection cannula. The mouse was then killed and the position of the dye determined (Nyemitei-Addo *et al.*, 1980). Dye injected into the third ventricle was not detected in the fourth ventricle. Likewise dye injected into the fourth ventricle did not seem to enter the third ventricle. Intravenous injections (0.20 ml/25 g) were made through a lateral tail vein and subcutaneous injections (0.25 ml/25 g) in the dorsal region of the neck. Δ^9-THC was mixed with two parts of Tween 80 by weight and then dispersed in 0.9% w/v NaCl solution (saline). The drug is only sparingly soluble in water and even in the presence of Tween 80 it was not possible to prepare homogeneous dispersions containing more than 20 μg of Δ^9-THC per μl of Tween 80/saline.

Deep body temperature was monitored with a thermistor probe (YSI 402) inserted 3 cm into the rectum. Changes in the rate of heat production were detected indirectly by the measurement of the oxygen consumption rate (V_{O_2}). This was measured over a 50 to 60 min period by the closed-circuit system described by Pertwee & Tavendale (1977) and was expressed as volume of oxygen consumed per 25 g body weight per hour after adjustment for s.t.p. Unless stated otherwise the ambient temperature was kept at 22°C. Throughout most experiments mice were kept in a restraining apparatus (Pertwee, 1974) and measurements of rectal temperature (t_R) and usually also of V_{O_2} were made every 2 min. However, in one series of experiments in which the effect of pretreatment with subcutaneous injections of Δ^9-THC on responses to subsequent intraventricular or intravenous injections of the drug was studied, mice were only held in the restraining apparatus while intraventricular or intravenous injections were made. At other times, except when held in the hand for measurement of t_R, the mice remained unrestrained at an ambient temperature of 22°C. In this series of experiments V_{O_2} was not determined and t_R was measured for 30 min before injection and over a 60 min period after injection. t_R was measured every 15 min when intraventricular injections were made and every 30 min when intravenous injections were made.

Differences between the means of experimental data have been evaluated by Student's t test ($P>$ or <0.05) and limits of error are expressed as standard errors.

Table 1 Effects of Δ^9-tetrahydrocannabinol (Δ^9-THC) on the rectal temperatures and oxygen consumption rates of groups of 6 restrained mice after injection into the preoptic area of the anterior hypothalamus (PO/AH) or into the third (III) or fourth (IV) cerebral ventricle.

Route	*Drug*	*Dose* (μg)	Δt_R (°C ± s.e.)	T_1 (min)	P_1	ΔV_{O_2} (ml 25 g^{-1} h^{-1} ± s.e.)	T_2 (min)	P_2
PO/AH	Δ^9-THC	5	−1.7 ± 0.2***	+28	<0.001	−19 ± 4	+2 to 12	<0.01
		10	−1.4 ± 0.2***	+22	<0.001	−30 ± 5	+2 to 12	<0.01
	Tween 80	20	−0.3 ± 0.2	+28	NS	−15 ± 5	+2 to 12	<0.05
		20	−0.2 ± 0.1	+22	NS	-	-	-
IV	Δ^9-THC	5	−1.3 ± 0.2*	+26	<0.01	−37 ± 9*	+2 to 12	<0.02
		10	−2.4 ± 0.3***	+20	<0.001	−62 ± 13**	+2 to 12	<0.01
	Tween 80	20	−0.6 ± 0.2	+26	<0.02	−13 ± 4	+2 to 12	<0.05
		20	−0.6 ± 0.2	+20	<0.02	-	-	-
III	Δ^9-THC	10	−1.9 ± 0.1***	+20	<0.001	−62 ± 7***	+2 to 12	<0.001
	Tween 80	20	−0.5 ± 0.1	+20	<0.02	−12 ± 4	+2 to 12	NS

The earliest times after injection of Δ^9-THC at which maximum changes in mean rectal temperature (Δt_R) or in mean oxygen consumption rate (ΔV_{O_2}) occurred are listed under T_1 and T_2 respectively. Digits listed under P_1 and P_2 are P values (paired t test) for differences between preinjection and minimum postinjection values of t_R and V_{O_2} respectively. Significant differences (unpaired t test) between the effects of Δ^9-THC and of Tween 80 injected by the same route on t_R (Δt_R at T_1) and on V_{O_2} (ΔV_{O_2} at T_2) are denoted by asterisks (*$P<0.05$; **$P<0.01$; ***$P<0.001$).

Results

Effects of intrahypothalamic, intraventricular and intravenous injection of Δ^9-THC at 22°C

Doses of 5 and 10 μg of Δ^9-THC given intrahypothalamically produced significant falls in both t_R and V_{O_2} (see Table 1). The falls produced by 10 μg were no greater than those produced by 5 μg. A dose of 10 μg also produced significant falls in t_R and V_{O_2} when Δ^9-THC was injected intraventricularly (see Table 1). Indeed the maximum changes in V_{O_2} produced by injection of this dose into the third or fourth ventricle were significantly larger than the corresponding changes observed after intrahypothalamic injection ($P<0.05$). The maximum changes in t_R produced by injection of Δ^9-THC (10 μg) into the fourth ventricle were also greater than those following intrahypothalamic injection ($P<0.02$). The hypothermia that followed injection of Δ^9-THC into the fourth ventricle was dose-related, 5 μg producing smaller falls in t_R than 10 μg ($P<0.02$). The accompanying falls in V_{O_2} varied considerably from mouse to mouse and the falls produced by 5 μg did not differ significantly from those elicited by 10 μg. The time courses of the falls in t_R and V_{O_2} produced by 10 μg of Δ^9-THC given intrahypothalamically or intraventricularly are shown in Figures 1, 2 and 3.

Irrespective of the route or dose of Δ^9-THC used, maximum falls in V_{O_2} occurred at earlier times after injection than maximum falls in t_R (see Figures 1, 2 and 3 and Tables 1 and 2). Falls in t_R were maximal at 18 to 28 min after injection whereas maximal falls in V_{O_2} occurred within 12 min of injection.

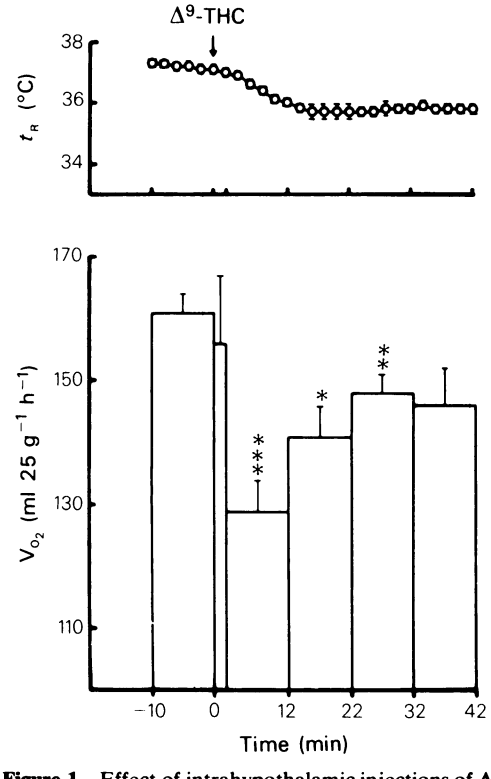

Figure 1 Effect of intrahypothalamic injections of Δ^9-tetrahydrocannabinol (Δ^9-THC, 10 μg) on the rectal temperature (t_R) and oxygen consumption rate (V_{O_2}) of 6 mice. Injections were made at time zero. Vertical lines show s.e. Asterisks denote significant differences (Student's t test for paired data) between preinjection and postinjection V_{O_2} values (*$P<0.05$; **$P<0.01$; ***$P<0.001$). Postinjection t_R values are significantly less than t_R at time zero from 4 min after time zero until the end of the experiment ($P<0.02$).

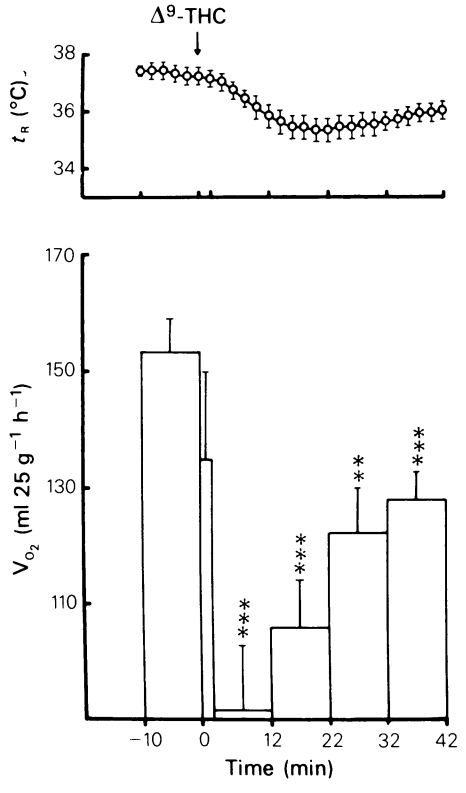

Figure 2 Effect of injections of Δ^9-tetrahydrocannabinol (Δ^9-THC, 10 μg) into the IIIrd cerebral ventricle on the rectal temperature (t_R) and oxygen consumption rate (V_{O_2}) of 6 mice. Injections were made at time zero. Vertical lines show s.e. Asterisks denote significant differences (Student's t test for paired data) between preinjection and postinjection V_{O_2} values (**$P<0.01$; ***$P<0.001$). Postinjection t_R values are significantly less than t_R at time zero from 6 min after time zero until the end of the experiment ($P<0.001$).

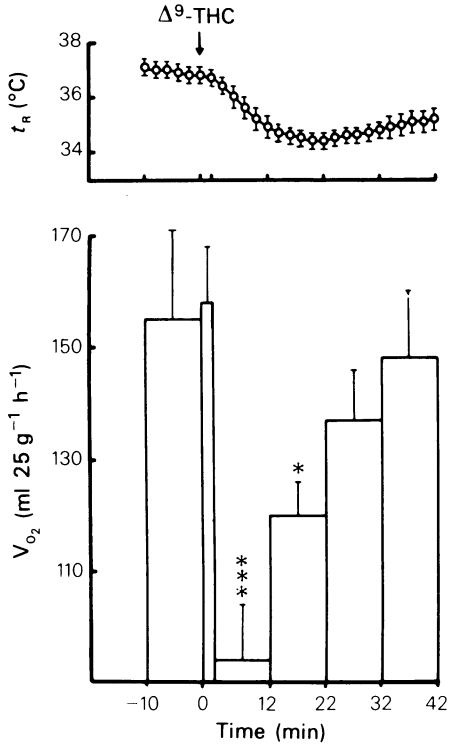

Figure 3 Effect of injections of Δ^9-tetrahydrocannabinol (Δ^9-THC, 10 μg) into the IVth cerebral ventricle on the rectal temperature (t_R) and oxygen consumption rate (V_{O_2}) of 6 mice. Injections were made at time zero. Vertical lines show s.e. Asterisks denote significant differences (Student's *t* test for paired data) between preinjection and postinjection V_{O_2} values. (*$P<0.05$; **$P<0.01$; ***$P<0.001$). Postinjection t_R values are significantly less than t_R at time zero from 4 min after time zero until the end of the experiment ($P<0.02$).

In some experiments the drug vehicle itself produced small but significant falls in t_R or V_{O_2} (see Table 1). Small falls in t_R (0.6 ± 0.1; $n=6$) were also observed in restrained mice with implanted cannula guides (above third ventricle) which had not received injections of either drug or vehicle. The falls in V_{O_2} following intrahypothalamic injection of Δ^9-THC were not significantly greater than those following injection of Tween 80. However, all of the other responses to intrahypothalamic and intraventricular injections of Δ^9-THC were significantly greater than the corresponding responses to the vehicle.

Doses of 5 to 7 μg of Δ^9-THC (0.25 mg/kg) given intravenously did not appear to affect thermoregulation. In this experiment the rectal temperatures of 6 restrained mice were monitored for 30 min before injection and over a 60 min period after injection. t_R fell gradually throughout the experiment and at the end of the postinjection period was 0.6 ± 0.1°C below its value at the time of injection. Although statistically significant ($P<0.01$) this fall was no greater than the fall in t_R which followed intravenous injection of Tween 80 at a dose of 0.5 mg/kg (0.6 ± 0.2°C; $n=6$).

Abolition of the effects of intraventricular injection of Δ^9-THC

In experiments with a group of 6 restrained mice it was found that at an ambient temperature of 32°C, 10 μg of Δ^9-THC injected into the fourth ventricle failed to lower either t_R or V_{O_2} (see Table 2). At 22°C, the same mice all showed marked falls in t_R and V_{O_2} in response to the same dose of the drug. Four of the mice had first received Δ^9-THC at an ambient temperature of 32°C and subsequently at 22°C. The other two animals had first received the drug at 22°C, and subsequently at 32°C.

The effects of intraventricular injection of Δ^9-THC could also be abolished in mice by first subjecting the animals to several subcutaneous injections of the drug. As shown in Table 3, mice which had been given a subcutaneous injection of Δ^9-THC (20 mg/kg) on days 1, 2 and 3 did not show any significant hypothermia in response to 10 μg of Δ^9-THC injected into the fourth ventricle on day 4. The same subcutaneous pretreatment with Δ^9-THC also rendered mice tolerant to the hypothermic effect of Δ^9-THC administered intravenously on day 4 at a dose of 2.0 mg/kg (see Table 3). Mice which had been pretreated with the drug vehicle (40 mg/kg) showed

Table 2 The influence of ambient temperature on the effect on rectal temperature and oxygen consumption rate of 10 μg Δ^9-tetrahydrocannabinol (Δ^9-THC) injected into the fourth ventricle of the restrained mouse ($n=6$)

Ambient temperature °C)	Δt_R (°C ± s.e.)	T_1 (min)	P_1	ΔV_{O_2} (ml 25 g^{-1}h^{-1} ± s.e.)	T_2 (min)	P_2
22	−2.5 ± 0.4†	+18	<0.01	−54 ± 8††	+2 to 12	<0.01
32	−0.3 ± 0.2	+18	NS	+3 ± 4	+2 to 12	NS

Symbols († $P<0.01$; †† $P<0.001$) denote significant differences (paired *t* test) between Δt_R or ΔV_{O_2} at 22°C and Δt_R or ΔV_{O_2} at 32°C. See also footnote to Table 1.

Table 3 The effect of subcutaneous pretreatment with Δ^9-tetrahydrocannabinol (Δ^9-THC) once daily for 3 days (20 mg/kg) on the hypothermic response of the unrestrained mouse ($n = 6$) to Δ^9-THC injected on the fourth day into either the fourth ventricle (10 μg i.c.v.) or a lateral tail vein (2.0 mg/kg i.v.)

Pretreatment on days 1, 2 and 3		*Treatment on day 4*				
Drug	*Dose (mg/kg)*	Drug	Route	Δt_R (°C ± s.e.)	T_1 (min)	P_1
Tween 80	40	Δ^9-THC	i.c.v.	−2.7 ± 0.3**	+15	< 0.001
Δ^9-THC	20	Δ^9-THC	i.c.v.	−0.9 ± 0.3	+15	NS
Tween 80	40	Δ^9-THC	i.v.	−1.5 ± 0.2***	+30	< 0.001
Δ^9-THC	20	Δ^9-THC	i.v.	+0.2 ± 0.2	+30	NS

See footnote to Table 1.

significant falls in t_R when given intraventricular or intravenous injections of Δ^9-THC on day 4. Just before intraventricular injection of Δ^9-THC on day 4 the mean rectal temperature of mice which had been pretreated with Δ^9-THC was 37.2 ± 0.3°C and the mean rectal temperature of Tween pretreated animals was 37.1 ± 0.2°C. Corresponding t_R values for animals about to be injected with Δ^9-THC intravenously were 36.9 ± 0.2°C and 36.3 ± 0.1°C respectively.

Discussion

Since injection of Δ^9-THC into the preoptic area of the anterior hypothalamus or into the third ventricle produced significant falls in body temperature and oxygen consumption rate and since the drug was effective intrahypothalamically at a dose (5 μg) that did not seem to alter thermoregulation when given intravenously, it would appear that Δ^9-THC may well be able to alter thermoregulation in the mouse by interacting with the thermoregulatory centres of the anterior hypothalamus. Other sites may also be involved. The size of the changes in body temperature and oxygen consumption produced by injection of Δ^9-THC into the fourth ventricle were of the same order as those produced by injection into the third ventricle. Since the fourth ventricle lies closer to the midbrain, pons and medulla oblongata, all of which are thought to have a role in thermoregulation, than to the thermoregulatory centres of the hypothalamus, it is possible that in mice as in rats and cats (Schmeling & Hosko, 1976; 1980), Δ^9-THC can act at extrahypothalamic sites within the brain as well as at hypothalamic sites to lower body temperature. Another possibility is that when Δ^9-THC is injected into the fourth ventricle it passes into the third ventricle and from there penetrates the hypothalamic thermoregulatory centres. Against this possibility however, is the observation that after methylene blue had been injected in the fourth ventricle, no dye was detected in the third ventricle.

The changes in thermoregulation produced by intrahypothalamic or intraventricular injection of Δ^9-THC showed several similarities to changes produced by intravenous administration of the drug (Pertwee & Tavendale, 1977). Firstly, there was evidence of a cause and effect relationship between reduced heat production and hypothermia. The drug-induced falls in oxygen consumption and hence presumably in heat production after injection of Δ^9-THC always occurred earlier than the falls in body temperature. Secondly, the drug appeared to act selectively on heat produced in response to cold since injection of Δ^9-THC into the fourth ventricle markedly lowered oxygen consumption at an ambient temperature of 22°C but failed to do so at 32°C. The oxygen consumption of restrained mice at 32°C is almost minimal (Pertwee & Tavendale, 1977) presumably because at this ambient temperature the animals do not need to produce large amounts of heat in order to maintain a balance between heat gain and heat loss. Finally, mice subjected to a series of subcutaneous injections of Δ^9-THC showed tolerance to the hypothermic effect of the drug when it was injected into the fourth ventricle. The same pretreatment also rendered mice tolerant to the hypothermic effect of intravenously administered Δ^9-THC. Taken together these observations suggest that Δ^9-THC can act centrally to alter thermoregulation not only after direct injection into the hypothalamus or cerebral ventricles but also after administration by peripheral routes. The finding that pretreatment with Δ^9-THC by a peripheral route produced tolerance to the hypothermic effect of intraventricularly administered drug also lends support to the hypothesis (Lawrence & Pertwee, 1973) that tolerance to the hypothermic effect of Δ^9-THC in mice 'does not depend on changes in the metabolism or distribution of Δ^9-THC leading to changes in brain levels of the drug and its metabolites'.

After intravenous administration of Δ^9-THC at a dose level (2.0 mg/kg) that can markedly lower the body temperature of restrained mice (Pertwee & Tavendale, 1977) concentrations of the drug in mouse brain have been reported to rise to peak values of about 0.5 μg per g of brain tissue (Gill & Jones, 1972). The wet weight of an adult mouse brain is approximately 450 mg and yet in our experiments doses of 5 μg (i.e. about 10 μg per g of brain tissue) given intrahypothalamically or intraventricularly produced only moderate falls in body temperature. There are at least two possible explanations for this apparent discrepancy. Firstly, Δ^9-THC when dispersed in a mixture of Tween 80 and saline is probably taken up by brain tissue far less readily after intraventricular or even intrahypothalamic injection than after intravenous injection (Gill & Lawrence, 1973). Secondly, a major metabolite of Δ^9-THC, 11-hydroxy-Δ^9-THC, is thought to contribute significantly towards the pharmacological activity of its parent compound when the latter is administered to mice intravenously (Gill, Jones & Lawrence, 1973). However, when the parent compound is given intracerebrally or intraventricularly this is probably not so since conversion of Δ^9-THC to its 11-hydroxy metabolite in mouse brain is thought to be negligible (Christensen, Freudenthal, Gidley, Rosenfeld, Boegli, Testino, Brine, Pitt & Wall, 1971).

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References

CHRISTENSEN, H.D., FREUDENTHAL, R.I., GIDLEY, J.T., ROSENFELD, R., BOEGLI, G., TESTINO, L., BRINE, D.R., PITT, C.G. & WALL, M.E. (1971). Activity of Δ^8- and Δ^9-tetrahydrocannabinol and related compounds in the mouse. *Science*, **172**, 165–167.

DASCOMBE, M.J. & MILTON, A.S. (1975). The effects of cyclic adenosine 3′,5′-monophosphate and other adenine nucleotides on body temperature. *J. Physiol.*, **250**, 143–160.

FITTON, A.G. & PERTWEE, R.G. (1981). Effects of intrahypothalamic and intracerebroventricular injections of Δ^9-tetrahydrocannabinol on thermoregulation in restrained mice. *Br. J. Pharmac.*, **74**, 873–874P.

GILL, E.W. & JONES, G. (1972). Brain levels of Δ^1-tetrahydrocannabinol and its metabolites in mice – correlation with behaviour, and the effect of the metabolic inhibitors SKF 525A and piperonyl butoxide. *Biochem. Pharmac.*, **21**, 2237–2248.

GILL, E.W., JONES, G. & LAWRENCE, D.K. (1973). Contribution of the metabolite 7-hydroxy-Δ^1-tetrahydrocannabinol towards the pharmacological activity of Δ^1-tetrahydrocannabinol in mice. *Biochem. Pharmac.*, **22**, 175–184.

GILL, E.W. & LAWRENCE, D.K. (1973). The distribution of Δ^1-tetrahydrocannabinol in the mouse brain after intraventricular injection. *J. Pharm. Pharmac.*, **25**, 948–952.

GILL, E.W., PATON, W.D.M. & PERTWEE, R.G. (1970). Preliminary experiments on the chemistry and pharmacology of cannabis. *Nature*, **228**, 134–136.

HAAVIK, C.O., COLLINS, F.G. & HARDMAN, H.F. (1975). Studies on the mechanisms of hypothermic action of tetrahydrocannabinols. In *Temperature Regulation and Drug Action*. ed. Lomax, P., Schönbaum, E. & Jacob, J. pp. 293–309, Basel: Karger.

HAAVIK, C.O. & HARDMAN, H.F. (1979). In *Body Temperature: Regulation, Drug Effects and Therapeutic Implications*. Chapter 20, ed. Lomax, P. & Schönbaum, E. New York: Marcel Dekker, Inc.

LAWRENCE, D.K. & PERTWEE, R.G. (1973). Brain levels of Δ^1-tetrahydrocannabinol and its metabolites in mice tolerant to the hypothermic effect of Δ^1-tetrahydrocannabinol. *Br. J. Pharmac.*, **49**, 373–4.

NYEMITEI-ADDO, I. & PERTWEE, R.G. (1981). Effects of intrahypothalamic injections of adenosine 3′,5′-monophosphate and dopamine on thermoregulation in restrained mice. *Br. J. Pharmac.*, **72**, 566–567P.

NYEMITEI-ADDO, I., PERTWEE, R.G. & TAVENDALE, R. (1980). Stereotaxic implantation of cannulae for subsequent drug administration into the third ventricles of conscious mice. *Br. J. Pharmac.*, **68**, 189P.

PATON, W.D.M. & PERTWEE, R.G. (1973). In *Marijuana: Chemistry, Pharmacology, Metabolism and Clinical Effects*. Chapter 5. ed. Mechoulam, R. New York: Academic Press.

PERTWEE, R.G. (1974). Tolerance to the effect of Δ^1-tetrahydrocannabinol on corticosterone levels in mouse plasma produced by repeated administration of cannabis extract or Δ^1-tetrahydrocannabinol. *Br. J. Pharmac.*, **51**, 391–397.

PERTWEE, R.G. & TAVENDALE, R. (1977). Effects of Δ^9-tetrahydrocannabinol on the rates of oxygen consumption of mice. *Br. J. Pharmac.*, **60**, 559–568.

SCHMELING, W.T. & HOSKO, M.J. (1976). Hypothermia induced by Δ^9-tetrahydrocannabinol in rats with electrolytic lesions of preoptic region. *Pharmac. Biochem. Behav.*, **5**, 79–83.

SCHMELING, W.T. & HOSKO, M.J. (1980). Hypothermic effects of intraventricular and intravenous administration of cannabinoids in intact and brainstem transected cats. *Neuropharmac.*, **19**, 567–573.

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