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EFFECTS OF Δ^9-TETRAHYDROCANNABINOL, 2.4-DINITROPHENOL AND PENTOLINIUM TARTRATE ON BEHAVIOURAL THERMOREGULATION IN MICE

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1 A new apparatus in which mice are allowed to shuttle between the warm and cool parts of a continuous oval tunnel has been designed for the measurement of drug effects on behavioural thermoregulation.

2 The length of time that untreated mice spent in the warmer part of the apparatus (tunnel wall temperature 38°C) was found to be inversely related to the temperature of the cooler part (wall temperature 18°, 24° or 30°C).

3 Mice treated with 2,4-dinitrophenol at a dose known to be hyperthermic at an ambient temperature of 32°C (20 mg/kg s.c.) spent an increased length of time in the cooler part of the apparatus (wall temperature 18°C) and did not exhibit any change in rectal temperature.

4 Mice treated with pentolinium tartrate at a dose known to be hypothermic at room temperature (5.0 mg/kg i.v.) spent a decreased length of time in the cooler part of the apparatus (wall temperature 24°C) and did not exhibit any change in rectal temperature.

5 It is concluded from the above results that the apparatus can be used to measure drug effects on behavioural thermoregulation.

6 In experiments of 30 min duration, mice treated with Δ^9-tetrahydrocannabinol (Δ^9-THC) at doses known to be hypothermic and to lower oxygen consumption at room temperature (20 mg/kg i.p. or 2.0 mg/kg i.v.) spent a longer time in the warmer part of the apparatus between 15 and 30 min after injection. Rectal temperatures measured 30 min after injection were only slightly less than those of control mice. In these experiments the wall temperature of the cool tunnel was 24°C.

7 In experiments of 15 min duration, mice treated with Δ^9-THC (20 mg/kg) and then placed in the apparatus spent more time in the cooler part of the apparatus (wall temperature 24°C) and exhibited a large fall in rectal temperature.

8 It is concluded that immediately after injection of Δ^9-THC the mice do not attempt to oppose drug-induced falls in deep body temperature by moving into a warm environment and that only later do the animals demonstrate a preference for a warm environment.

Introduction

There is evidence (Pertwee & Tavendale, 1977) that decrease in heat production in mice given Δ^9-tetrahydrocannabinol (Δ^9-THC) contributes significantly towards the hypothermic effect of this drug. The present study was undertaken to determine whether hypothermic doses of Δ^9-THC also induce detectable changes in behavioural thermoregulation.

Several studies have been made of drug effects on behavioural thermoregulation in rodents (e.g. Avery & Penn, 1973; Yehuda & Wurtman, 1974; Polk & Lipton, 1975; Cox, Green & Lomax, 1975). In these studies, behavioural thermoregulation was monitored over discrete intervals that started at times ranging from 10 to 60 min after drug injection. It was decided to develop a new method in which the effects of drugs on the behavioural thermoregulation of a single animal could be monitored continuously in a quantitative manner starting immediately after drug injection. This was firstly to detect early changes in behaviour associated with thermoregulation and secondly to distinguish these from any subsequent changes associated, for example, with recovery from some drug-induced change. The new method was also to be as direct a measure of behavioural thermoregulation as possible.

This paper describes the new method and initial experiments to test its usefulness in measuring drug effects on behavioural thermoregulation. Some of

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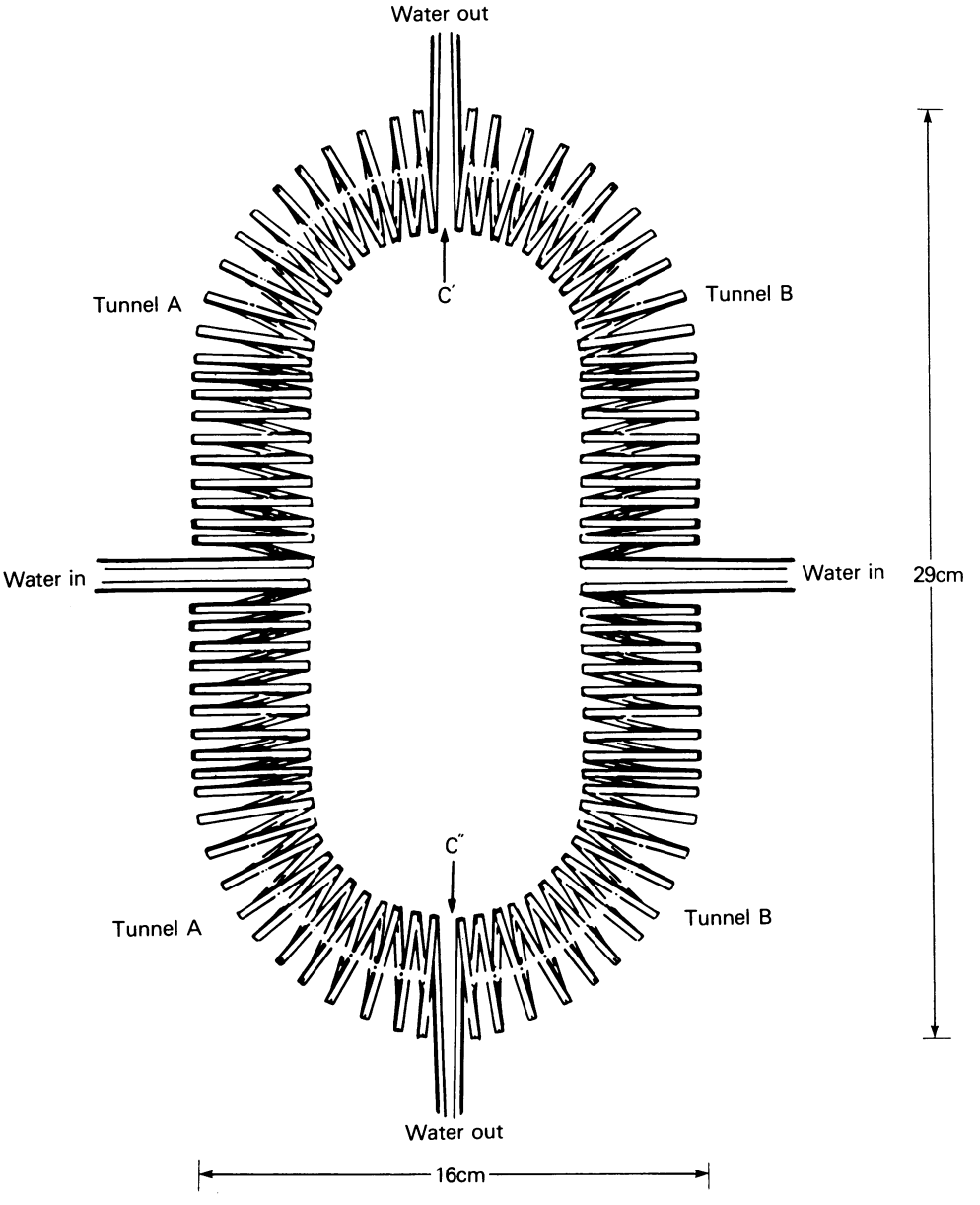

Figure 1 Diagram of the apparatus which was designed to measure drug effects on behavioural thermoregulation. Not drawn to scale. (For further description—see text.)

Table 1 Air temperatures within the tunnels A and B and at the junctional positions C′ and C″

Wall temperature (°C)		*Air temperature* (°C)		
A	*B*	*In A*	*In B*	*At C′ and C″*
38	18	35.7 to 36.8	22.5 to 23.3	33.2 to 33.8
38	24	35.6 to 36.4	26.8 to 27.3	33.4 to 34.9
38	30	35.6 to 36.6	30.3 to 30.5	34.1 to 34.9

these experiments were carried out with 2,4-dinitrophenol (DNP), a hyperthermic agent (Shemano & Nickerson, 1963) and others with the ganglion blocking compound (Mason & Wien, 1955) pentolinium tartrate which can induce hypothermia in mice (Tavendale, unpublished). Finally, experiments with Δ^9-THC are described.

A brief account of the method described in this paper and the results obtained from experiments with DNP were presented at the 7th International Congress of Pharmacology (Pertwee, Tavendale & Michel, 1978).

Methods

Behavioural thermoregulation was measured by the use of a newly designed apparatus. The apparatus, shown in Figure 1, consisted of two 'U' shaped tunnels A and B (i.d. 3.3 cm). Each was made of copper/nickel tubing (o.d. 4.8 mm) wound spirally (44 turns per tunnel). Water was circulated through the tubing by two Churchill Laboratory LTCV Thermocirculators. This allowed the walls of the two tunnels to be maintained at different temperatures. The temperature of the water that entered each tunnel wall was regularly monitored. The tunnels were kept in an environmental chamber, at a temperature of 31 to 32°C. During experiments a mouse was placed in one of the tunnels and the two tunnels were then held together to form a continuous oval. The mouse could now shuttle between the warm tunnel, A, and the cool tunnel, B. In all experiments the wall temperature of the warm tunnel was 38°C. The wall temperature of the cool tunnel was usually 24°C. However, in the experiments with DNP it was 18°C and in some experiments with untreated mice it was kept at 18°, 24° or 30°C. Table 1 shows the temperature of the air within the two tunnels and at the junctions (shown in Figure 1 as C′ and C″) between them.

Behavioural thermoregulation was monitored by noting the times spent by a mouse in each tunnel. Times during which the torso of the mouse was positioned across either of the junctions between the two tunnels were recorded separately and will be referred to as times spent at C. A bar was fixed horizontally at each of the two junctions C′ and C″. The height of the bar was adjusted so that it allowed mice to pass beneath it but minimized the time they spent at these junctional positions.

Trials started when the mouse was placed in the apparatus. Scoring of behaviour began 1 min later so that for example, in a 30 min trial, behaviour was observed over a 29 min period. Rectal temperatures were measured immediately before and after each trial by insertion of a thermistor probe (Y.S.I. 402) 3 cm into the rectum. In drug experiments, two mice, one assigned to a drug group and the other to a control group were each subjected in turn to a preinjection trial, one immediately after the other. The same two mice were then each subjected to a postinjection trial beginning immediately after injection. This procedure was repeated until 6 drug-treated and 6 control mice had been tested. Between trials, mice were kept at room temperature (20 to 22°C). To test whether drug-induced changes in behaviour might reflect a drug effect on locomotor activity, during all trials a record was kept of the number of times (locomotor score) mice crossed the junctional positions C′ or C″.

All experiments were carried out with adult male mice (LACA derived MF1 strain) weighing 28 to 35 g.

Dinitrophenol (DNP) was dissolved in a 15 mg/ml aqueous solution of $NaHCO_3$ (Tainter & Cutting, 1933) and injected subcutaneously into the dorsal neck region. Control injections were made with the aqueous solution of $NaHCO_3$. Pentolinium tartrate was dissolved in a 9 mg/ml NaCl solution (saline) and was injected intravenously. Control injections were made with saline. Δ^9-THC was mixed with 2 parts of Tween 80 by weight and then dispersed in saline. The drug was injected either intraperitoneally or intravenously. Control injections contained doses of Tween 80 equal to those used in the corresponding drug injections.

The dose of DNP (20 mg/kg) used in our experiments was one known (Tavendale, unpublished) to induce hyperthermia and elevate oxygen consumption in mice kept at ambient temperatures of 32°C. The dose (5.0 mg/kg) of pentolinium tartrate chosen was one which induces hypothermia in mice at room temperature. The treatments (20 mg/kg i.p. and 2.0 mg/kg i.v.) used in the experiments with Δ^9-THC were ones previously found (Pertwee & Tavendale, 1977) to reduce the rectal temperature and oxygen consumption of mice kept at 22°C. In all experiments, the volume injected was either 0.25 ml/25 g (i.p. and s.c.) or 0.20 ml/25 g (i.v.).

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

Results

Effects of tunnel wall temperature on the behaviour and rectal temperature of untreated mice subjected to 30 min trials

Figure 2 shows that the lower the wall temperature of the cooler part of the apparatus, the greater the length of time spent by mice in the warm tunnel and,

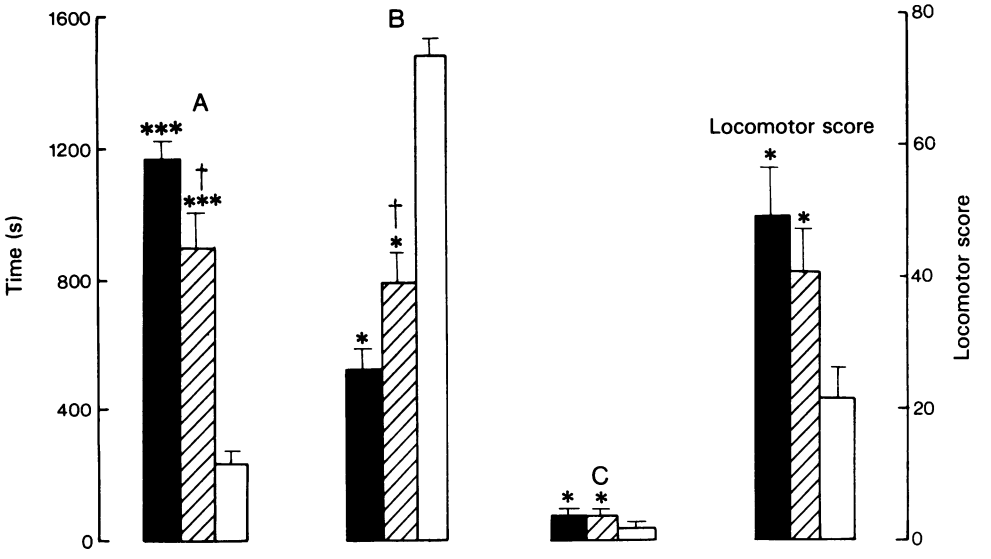

Figure 2 Behaviour during 30 min trials in which the wall temperature of tunnel A was 38°C and of B was either 18°C (solid columns) or 24°C (hatched columns) or 30°C (open columns). The figure shows the mean times spent by groups of 6 mice in A and B and at C and also the locomotor scores of the mice. Vertical lines show s.e. For each of these parameters, the significance (unpaired t test) of differences between values observed when the wall temperature of B was 30°C and values observed when this wall temperature was 24° or 18°C are shown by asterisks (*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$). The significance of differences between values observed at the two lower wall temperatures of B (18° and 24°C) are denoted by † ($P < 0.05$).

correspondingly, the less time spent by the mice in the cool tunnel. For example, when the wall temperature of the cool tunnel was 30°C, the mean length of time spent by mice in the warm tunnel (wall temperature 38°C) was 229 ± 41 s. However, when the walls of the cool tunnel were kept at the lower temperatures 24° or 18°C, times spent in the warm tunnel were respectively 894 ± 98 and 1155 ± 64 s. The wall temperature of the cool tunnel also affected the mean locomotor score and the length of time spent at C. Both parameters were significantly less when this temperature was 30°C than at either 24° or 18°C. Although changes in the wall temperature of the cool tunnel affected behaviour in the apparatus, they did not affect rectal temperatures. The latter, measured immediately after the mice had been removed from the apparatus ranged from 36.8 ± 0.2°C (wall temperature of cool tunnel 30°C) to 37.4 ± 0.3°C (wall temperature of cool tunnel 18°C). However, in other experiments in which mice were restricted to the warm tunnel (wall temperature 38°C), rectal temperatures rose significantly ($P < 0.001$) during the 30 min trials from 37.7 ± 0.1°C to 39.1 ± 0.2°C. Conversely, when mice were restricted to the cool tunnel (wall temperature 24°C), rectal temperature fell significantly ($P < 0.001$) during the trials from 37.8 ± 0.2° to 36.4 ± 0.2°C. The post-trial rectal temperatures of the mice that had been restricted to the cool tunnel were significantly ($P < 0.001$) less than those of the mice kept in the warm tunnel.

Effects of 2,4-dinitrophenol on the behaviour and rectal temperature of mice subjected to 30 min trials

Figure 3 shows that mice which had been given DNP spent significantly more time (1160 ± 124 s) in the cooler part of the apparatus (wall temperature 18°C) than they had done in the preinjection trials (593 ± 94 s). In contrast, mice given the drug vehicle (see Figure 4) spent 379 ± 51 s in the cool tunnel, significantly less than the time (609 ± 97 s) these mice had spent there previously. After injection, both the drug and the control groups showed similar locomotor scores and spent similar lengths of time at C and both groups exhibited significantly less locomotor activity than in the preinjection trials.

Table 2 shows that the mean rectal temperature of the drug group (36.8 ± 0.4°C) did not change significantly during the postinjection trials, and was not significantly different from that of the control group (37.1 ± 0.2°C). The control group did show a significant rise in rectal temperature during the postinjec-

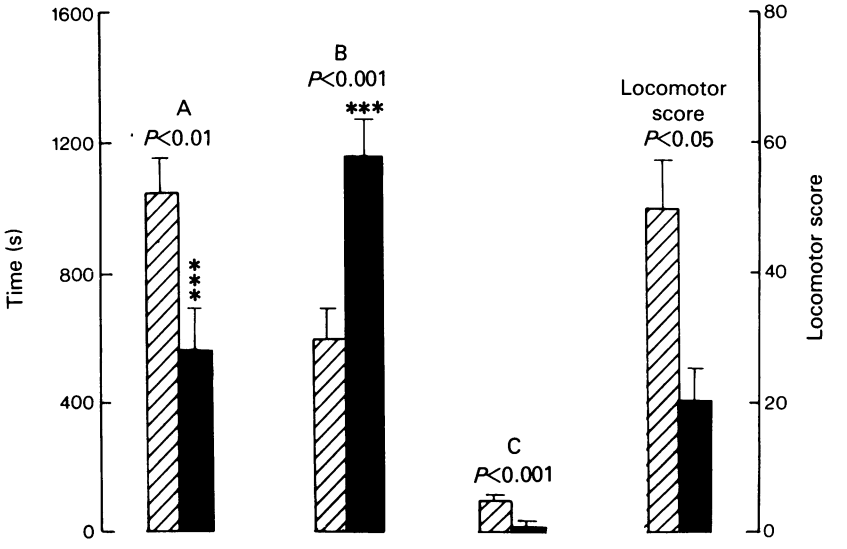

Figure 3 Behaviour in the apparatus during trials of 30 min duration before and after injection of 2,4-dinitrophenol (DNP, 20 mg/kg s.c.). The wall temperatures of A and B were respectively 38°C and 18°C. The figure shows the mean times spent by groups of 6 mice in A and B and at C in preinjection (hatched columns) and postinjection (solid columns) trials. Mean locomotor scores before and after injection are also shown. Vertical lines show s.e. Where significant, ($P < 0.05$), P values (Student's t test for paired data) for differences between preinjection and postinjection trial values are given. The significance (unpaired t test) of differences between drug and vehicle treatments are also shown (*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$).

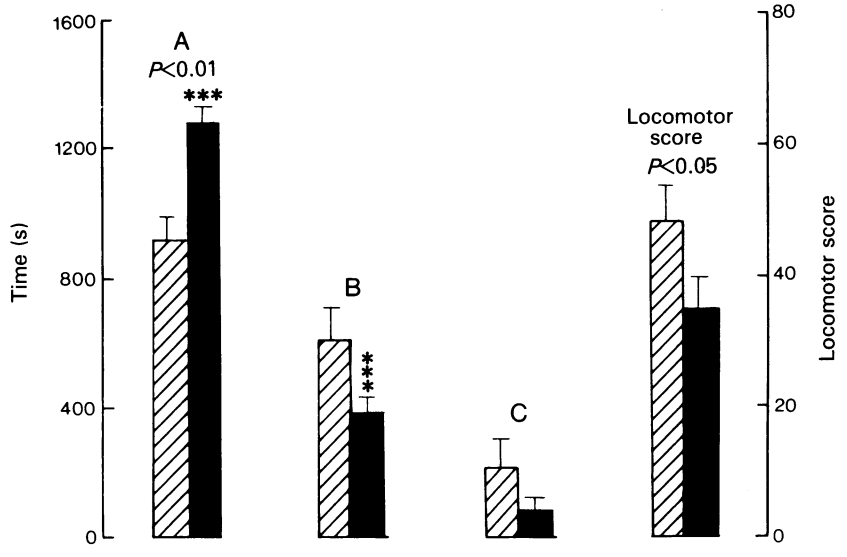

Figure 4 Behaviour in the apparatus during trials of 30 min duration before and after injection of 1.5% aqueous $NaHCO_3$ (0.25 ml/25 g i.p.). See also legend to Figure 3.

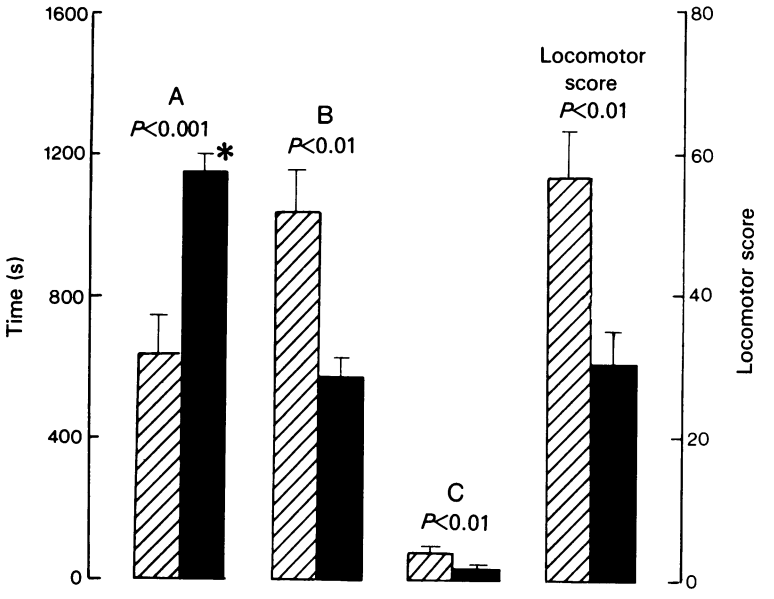

Figure 5 Behaviour in the apparatus during trials of 30 min duration before and after injection of pentolinium tartrate (5.0 mg/kg i.v.). The wall temperatures of A and B were respectively 38°C and 24°C. See also legend to Figure 3.

Table 2 Mean rectal temperatures (±s.e.) of groups of 6 mice before and after injection of 2,4-dinitrophenol (DNP, 20 mg/kg s.c.), pentolinium tartrate (5.0 mg/kg i.v.) and of the drug vehicles

Treatment	*Parameter*	*Preinjection trial*	*Postinjection trial*
DNP	t_{R0}	36.9 ± 0.5	36.0 ± 0.3
	t_{R30}	37.6 ± 0.3	36.8 ± 0.4
	P_1	NS	NS
$NaHCO_3$	t_{R0}	36.4 ± 0.4	36.0 ± 0.2
	t_{R30}	37.4 ± 0.3	37.1 ± 0.2
	P_1	<0.05	<0.02
	P_2	NS	NS
Pentolinium tartrate	t_{R0}	37.5 ± 0.1	36.7 ± 0.3
	t_{R30}	37.2 ± 0.1	36.7 ± 0.2
	P_1	NS	NS
Saline	t_{R0}	37.5 ± 0.4	37.2 ± 0.2
	t_{R30}	37.3 ± 0.2	37.0 ± 0.2
	P_1	NS	NS
	P_2	NS	NS

t_{R0} and t_{R30} denote mean rectal temperatures immediately before and after 30 min preinjection and postinjection trials. P_1 denotes P values (paired t test) for differences between t_{R0} and t_{R30} values. P_2 denotes P values (unpaired t test) for differences between drug and vehicle t_{R30} values.

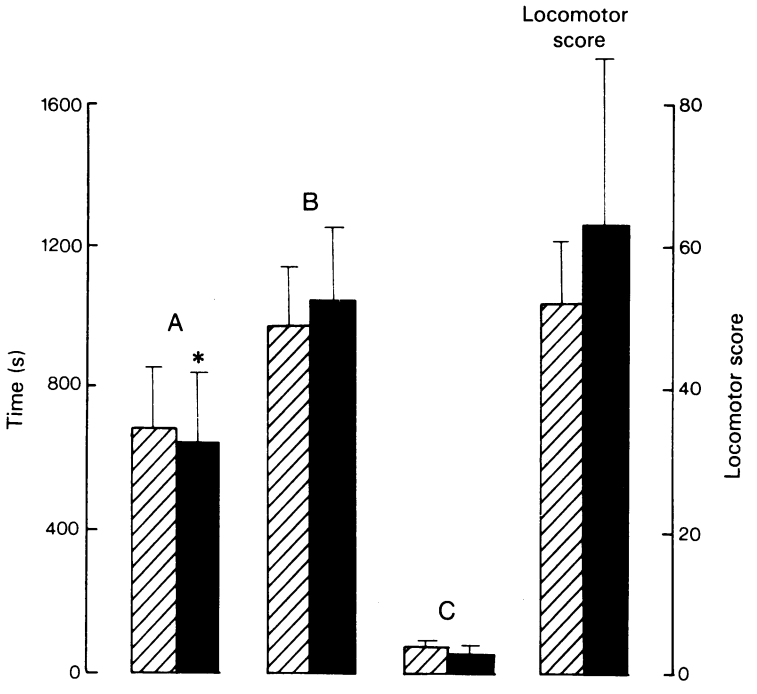

Figure 6 Behaviour in the apparatus during trials of 30 min duration before and after injection of saline (0.25 ml/25 g i.p.). The wall temperatures of A and B were respectively 38°C and 24°C. See also legend to Figure 3.

tion trials but had also done so in the preinjection trials. After mice had been restricted to the warm tunnel (38°C) rectal temperatures were significantly greater in mice which had received DNP (40.1 ±0.1°C) than in controls (38.9 ± 0.2°C).

Effects of pentolinium tartrate on the behaviour and rectal temperature of mice subjected to 30 min trials

Figure 5 shows that when the wall temperature of the cool tunnel was kept at 24°C, mice which had received pentolinium tartrate spent significantly more time (1141 ± 51 s) in the warmer part of the apparatus (38°C) than they had done previously (631 ± 111 s). Mice given saline (see Figure 6) spent similar lengths of time in the warm tunnel before (687 ± 166 s) and after (643 ± 198 s) injection. The drug and control groups of mice did not spend significantly different lengths of time at C either before or after injection. The locomotor score fell significantly after injection of pentolinium tartrate but not after saline.

Table 2 shows that neither the drug nor the control groups of mice experienced any significant change in rectal temperature during the postinjection trials and did not differ from each other. However, after mice had been restricted to the cooler part of the apparatus, rectal temperatures were significantly ($P < 0.001$) less in mice which had received pentolinium tartrate (32.1 ± 0.3°C) than in saline controls (36.5 ± 0.3°C).

Effects of Δ^9-tetrahydrocannabinol (20 mg/kg i.p.) on the behaviour and rectal temperature of mice subjected to 15 min trials

It was found (see Figure 7) that mice which had received Δ^9-THC spent significantly more time (767 ± 32 s) in the cooler tunnel (wall temperature 24°C) after injection than in their preinjection trials (460 ± 26 s). In contrast, mice given Tween 80 (see Figure 8) spent approximately similar lengths of time in the cooler part of the apparatus before (502 ± 28 s) and after injection (602 ± 73 s), although the postinjection difference between drug and control groups was not significant. The drug and the control groups had similar locomotor scores and spent similar lengths of time at C. Both groups of mice exhibited less locomotor activity and spent less time at C in their postinjection trials.

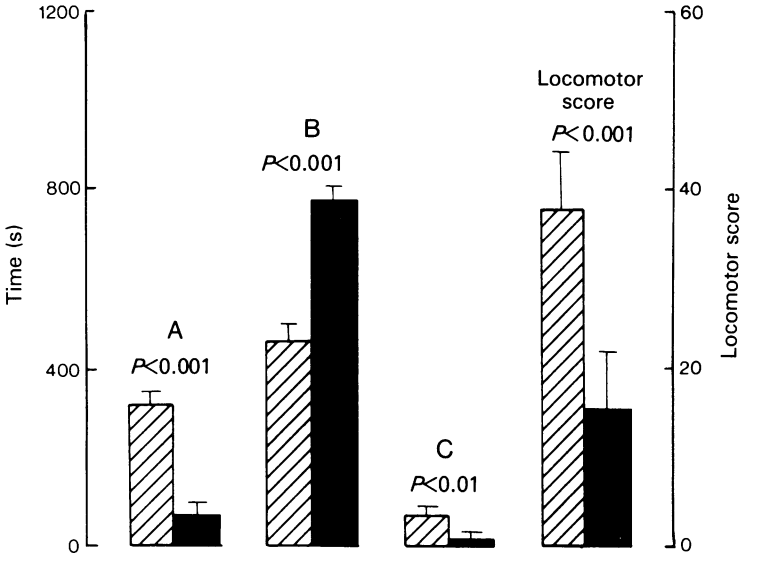

Figure 7 Behaviour in the apparatus during trials of 15 min duration before and after injection of Δ^9-tetrahydrocannabinol (Δ^9-THC 20 mg/kg i.p.). The wall temperatures of A and B were respectively 38°C and 24°C. See also legend to Figure 3.

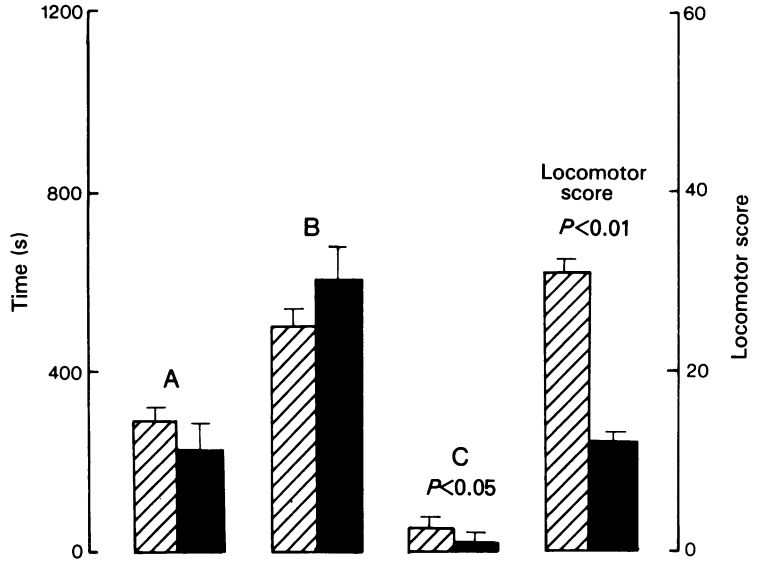

Figure 8 Behaviour in the apparatus during trials of 15 min duration before and after injection of Tween 80 in saline (40 mg/kg i.p.). The wall temperatures of A and B respectively 38°C and 24°C. See also legend to Figure 3.

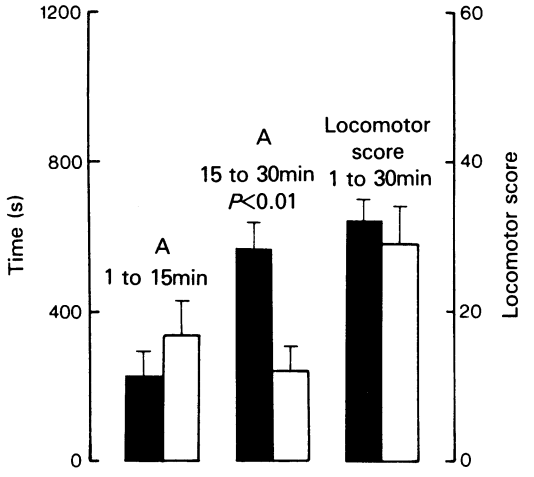

Figure 9 Behaviour in the apparatus during trials of 30 min duration after intraperitoneal injection of Δ^9-tetrahydrocannabinol (Δ^9-THC) at a dose of 20 mg/kg (solid columns) or of Tween 80 at a dose of 40 mg/kg (open columns). The wall temperatures of A and B were respectively 38°C and 24°C. The figure shows the mean time spent in A by groups of 6 mice from 1 to 15 min and from 15 to 30 min after injection. Mean locomotor scores recorded between 1 and 30 min after injection are also shown. Vertical lines show s.e. Where significant, ($P < 0.05$), P values (Student's t test for unpaired data) for differences between drug and control values are given.

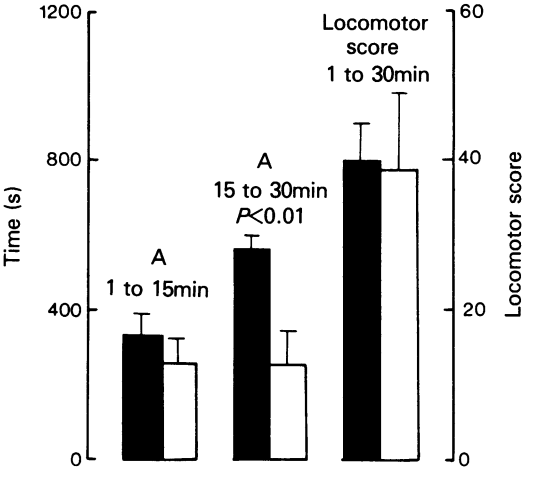

Figure 10 Behaviour in the apparatus during trials of 30 min duration after intravenous injection of Δ^9-tetrahydrocannabinol (Δ^9-THC) at a dose of 2.0 mg/kg (solid columns) or of Tween 80 at a dose of 4.0 mg/kg (open columns). See also legend to Figure 9.

Table 3 shows that the mice injected with Δ^9-THC developed a significant hypothermia in which rectal temperatures fell from 36.7 ± 0.1° to 32.8 ± 0.4°C. Mice given Tween 80 showed no significant change in rectal temperature. During the preinjection trials both groups of mice developed a significant hyperthermia.

Effects of Δ^9-tetrahydrocannabinol on the behaviour and rectal temperature of mice subjected to 30 min trials

Figures 9 and 10 and Table 4 show that in the 30 min trials, in contrast to the results obtained in the 15 min trials, mice which had been given Δ^9-THC either intraperitoneally (20 mg/kg) or intravenously (2.0 mg/kg) did not spend an increased length of time in the cool part of the apparatus (wall temperature 24°C). On the contrary they spent more time in the warm tunnel (wall temperature 38°C), but only in the final 15 min. In the first 15 min after injection, no significant effects were detected. After intraperitoneal

Table 3 Mean rectal temperatures (±s.e.) of groups of 6 mice before and after injection of Δ^9-tetrahydrocannabinol (Δ^9-THC, 20 mg/kg i.p.) or Tween 80 (40 mg/kg i.p.)

Treatment	*Parameter*	*Preinjection trial*	*Postinjection trial*
Δ^9-THC	t_{R0}	36.8 ± 0.1	36.7 ± 0.1
	t_{R15}	37.5 ± 0.1	32.8 ± 0.4
	P_1	<0.01	<0.001
Tween 80	t_{R0}	36.7 ± 0.2	36.6 ± 0.2
	t_{R15}	37.5 ± 0.1	37.0 ± 0.3
	P_1	<0.02	NS
	P_2	NS	<0.001

t_{R0} and t_{R15} denote mean rectal temperatures immediately before and after 15 min preinjection and postinjection trials. P_1 denotes P values (paired t test) for differences between t_{R0} and t_{R15} values. P_2 denotes P values (unpaired t test) for differences between drug and vehicle t_{R15} values.

injection of Δ^9-THC, the proportion of time spent in the warm tunnel during the second part of the post-injection trials (63 ± 8%) was significantly greater not only than in the first part (26 ± 9%) but also than the proportion during the whole of the preinjection trials (39 ± 9%). Control mice did not change the proportions of time spent in the warm tunnel.

Table 5 shows that at the end of the postinjection trials the rectal temperatures of mice given Δ^9-THC either intraperitoneally or intravenously were not significantly different from those measured immediately before drug injection. However, in both groups of drug-treated mice temperatures were significantly lower than in the corresponding controls.

Finally, no significant effects of Δ^9-THC either on locomotor scores or on times spent by mice at C were detected when drug and control groups were compared. Both groups exhibited less locomotor activity after injection.

Table 4 Proportion (% ± s.e.) of time spent by mice in the warm (A) and cool (B) parts of the apparatus before and after injection of Δ^9-tetrahydrocannabinol (Δ^9-THC, 20 mg/kg i.p. or 2.0 mg/kg i.v.) or Tween 80 (40 mg/kg i.p. or 4.0 mg/kg i.v.)

Treatment	*Parameter* (%)	*Preinjection trial* 1–30 min	*Postinjection trial* 1–15 min	15–30 min	P_1	P_2	P_3
Δ^9-THC (i.p.)	Time in A	39 ± 9	26 ± 9	63 ± 8	NS	<0.05	<0.01
Tween 80		37 ± 6	40 ± 11	27 ± 7	NS	NS	NS
Δ^9-THC (i.p.)	Time in B	59 ± 9	73 ± 9	35 ± 9	NS	NS	<0.01
Tween 80		60 ± 7	58 ± 11	70 ± 8	NS	NS	NS
Δ^9-THC (i.v.)	Time in A	28 ± 4	39 ± 8	62 ± 4	NS	<0.001	NS
Tween 80		28 ± 4	29 ± 8	28 ± 10	NS	NS	NS
Δ^9-THC (i.v.)	Time in B	68 ± 5	60 ± 8	35 ± 4	NS	<0.001	NS
Tween 80		68 ± 5	68 ± 8	70 ± 10	NS	NS	NS

For each group of mice, (1) P_1 denotes P values (paired t test) for differences observed between the behaviour of the mice in their preinjection trials (1 to 30 min) and in the first part (1 to 15 min) of their postinjection trials; (2) P_2 denotes the corresponding values in the second part (15 to 30 min) of their postinjection trials; (3) P_3 denotes P values for differences observed between behaviour in the first (1 to 15 min) and second part (15 to 30 min) of their postinjection trials.

Table 5 Mean rectal temperatures (±s.e.) of groups of 6 mice before and after injection of Δ^9-tetrahydrocannabinol (Δ^9-THC, 20 mg/kg i.p. or 2.0 mg/kg i.v.) or Tween 80 (40 mg/kg i.p. or 4.0 mg/kg i.v.)

Treatment	*Parameter*	*Preinjection trial*	*Postinjection trial*
Δ^9-THC (i.p.)	t_{R0}	37.0 ± 0.4	36.7 ± 0.4
	t_{R30}	37.2 ± 0.3	36.0 ± 0.3
	P_1	NS	NS
Tween 80 (i.p.)	t_{R0}	37.3 ± 0.4	36.8 ± 0.2
	t_{R30}	37.4 ± 0.4	37.1 ± 0.3
	P_1	NS	NS
	P_2	NS	<0.05
Δ^9-THC (i.v.)	t_{R0}	37.0 ± 0.5	36.2 ± 0.2
	t_{R30}	36.9 ± 0.1	36.3 ± 0.1
	P_1	NS	NS
Tween 80 (i.v.)	t_{R0}	37.1 ± 0.3	36.6 ± 0.1
	t_{R30}	37.3 ± 0.2	36.9 ± 0.2
	P_1	NS	NS
	P_2	NS	<0.05

t_{R0} and t_{R30} denote mean rectal temperatures immediately before and after 30 min preinjection and postinjection trials. P_1 denotes values (paired t test) for differences between t_{R0} and t_{R30} values. P_2 denotes P values (unpaired t test) for differences between drug and vehicle t_{R30} values.

Discussion

It was found that untreated mice shuttled repeatedly between the warm and cool parts of the apparatus. The results suggested that this behaviour constituted a form of thermoregulation and that measurement of the length of time spent in each part of the apparatus would indeed provide a quantitative measure of behavioural thermoregulation. The length of time the mice spent in the warm tunnel was inversely related to the wall temperatures of the cool tunnel. Furthermore, the post-trial deep body temperatures of the mice were the same irrespective of the wall temperature of the cool tunnel. Changes in deep body temperature were only observed when mice had been restricted to either one of the two tunnels.

It should be noted that of the four wall temperatures used in our experiments with untreated mice, the animals seemed to prefer the wall temperature of 30°C. Next in order of preference were 38° and 24°C and then 18°C. This preference is perhaps not unexpected since a temperature of 30°C lies only just below a range (31° to 32°C) reported to be thermally neutral for mice normally kept at room temperature (Herrington, 1940). Within this temperature range mice can keep their deep body temperatures constant without the need for large increases in heat production or heat loss.

The results obtained in the experiments with DNP and pentolinium suggest that the new method can provide a satisfactory measure of drug effects on behavioural thermoregulation. Shemano & Nickerson (1963) reported that the hyperthermic effect of DNP is probably the result of a peripherally mediated thermogenic action. We predicted therefore that mice treated with a hyperthermic dose of DNP would seek a cold environment and avoid a warm one. This type of behaviour was indeed observed. Furthermore, the mice did not exhibit any change in rectal temperature except when they were restricted to the warmer part of the apparatus.

The hypothermic effect of pentolinium tartrate in mice is at least partly due to increased heat loss from the body surface which in turn is probably due to a drug-induced peripheral vasodilatation (Tavendale, unpublished). Pentolinium is a bisquaternary ammonium compound and would therefore be expected to penetrate the blood brain barrier only at a very low rate. Consequently, its effects on body temperature which are rapid in onset are probably due mainly to its ganglion blocking action rather than to some less direct action mediated, for example by the central nervous system. It was predicted therefore that mice treated with a hypothermic dose of pentolinium tartrate would select a warm environment and avoid a cold one. Such behaviour was observed, the mice spending longer in the warmer part of the apparatus. They did not become hypothermic, unless they were restricted to the cooler part of the apparatus.

Mice which had been injected with a dose of Δ^9-THC known to be hypothermic at room temperature did not immediately attempt to prevent hypothermia by moving into a warm environment, but allowed their deep body temperatures to fall. This behaviour contrasts markedly with that of mice given a hypothermic dose of pentolinium and suggests that Δ^9-THC can impair thermoregulation not only by reducing heat production in the cold (Pertwee & Tavendale, 1977) but also by affecting behavioural thermoregulation. The mechanisms responsible for this effect have still to be elucidated. One possibility is that the drug acts directly on some central or peripheral thermoregulatory pathway. However, Δ^9-THC has numerous effects on behaviour (see review by Paton & Pertwee, 1973) and it is equally possible that the changes in behavioural thermoregulation are caused indirectly by some quite different behavioural action of the drug. In view of this possibility it should be noted that Δ^9-THC can reduce spontaneous motor activity in mice (Garriott, King, Forney & Hughes, 1967). However, in our experiments the mice treated with Δ^9-THC moved about the apparatus to the same extent as control mice. It is unlikely therefore that the changes in rectal temperature and behaviour observed after treatment with Δ^9-THC were merely reflecting a drug-induced reduction of spontaneous motor activity.

Finally, it was found that although mice did not move into the warmer part of the apparatus immediately after injection of Δ^9-THC, they did spend increased lengths of time in this part of the apparatus in the period between 15 and 30 min after drug treatment. Whether this apparent preference for a warm environment represents a direct effect of the drug is not clear. It might equally well indicate that the mice were already recovering from the effects of Δ^9-THC and were attempting to reverse hypothermia experienced during the first few minutes after injection of the drug.

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