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Cardiovascular and respiratory effects of cannabis in cat and rat

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Summary

1. In anaesthetized rats, intravenous administration of cannabis extract (10 mg/kg), Δ^1-tetrahydrocannabinol (THC) (0·5 mg/kg) and Δ^6-THC (0·5 mg/kg) caused a reduction in systemic blood pressure, pulse rate and respiratory rate.

2. Neither cannabinol (1 mg/kg, i.v.) nor cannabidiol (1 mg/kg, i.v.) had any observed effects on the cardiovascular and respiratory systems of the rat.

3. Pretreatment of rats with atropine (1 mg/kg, i.v.) reduced the hypotension and bradycardia caused by Δ^1-THC or the extract.

4. In anaesthetized cats with autoperfused hindquarters, cannabis extract (10 mg/kg, i.v.) and Δ^1-THC (0·2 mg/kg, i.v.) caused hypotension, bradycardia, depression of respiratory rate and reduction of hindlimb perfusion pressure.

5. Both cannabis extract and Δ^1-THC potentiated reflex vasodilatation and direct vasoconstriction in the hindlimb induced by intravenous noradrenaline in the cat ; they reduced reflex hindlimb vasoconstriction elicited by histamine, acetylcholine or bilateral carotid occlusion.

6. Tolerance to these cardiovascular and respiratory effects of cannabis extract developed in rats which had been treated i.p. with the extract at (50 mg/kg) per day for 14 days.

Introduction

Tolerance to the effects of tetrahydrocannabinols (THC) has been demonstrated in a variety of laboratory animals. Thus Ford & McMillan (1971) demonstrated a progressive reduction of the inhibitory effect on key pecking in pigeons with repeated administration of either Δ^1- or Δ^6-THC. Tolerance to Δ^1-THC has been reported in pigeons and rats in tests such as bar pressing behaviour (Ford & McMillan, 1971), in the conditioned shock avoidance test in rats (Bailey, Pradhan & Ghosh, 1971), and in locomotor activity in neonatal chicks (Abel, 1972).

Cannabis, particularly Δ^1-THC depresses blood pressure (Cavero & Jandhyala, 1972 ; Hosko & Hardman, 1971) pulse rate (Cavero & Jandhyala, 1972 ; Hosko & Hardman, 1971 ; Milzoff, Marts & Harger, 1971) and respiratory rate (Hosko & Hardman, 1971 ; Milzoff *et al.*, 1971) in various species including rat, cat and dog. We have investigated the effects of cannabis extract and various purified con-

stituents of cannabis on the cardiovascular and respiratory systems of rats and cats, and whether tolerance to the actions of cannabis would develop in rats after pre-treatment with the drug for 14 days.

Methods

Anaesthetized rats

Female rats of the Sprague-Dawley strain weighing 180 to 220 g were anaesthetized with 25% (w/v) urethane (12·5 g/kg) injected intraperitoneally. The trachea was cannulated with a pneumotachograph which was connected to an 'Ether' differential gas pressure transducer, the signal from which, after amplification by a Devices DC2C unit, was integrated by a Devices T3030 module to provide a record of respiratory tidal volume. Respiratory frequency was counted from this trace. Arterial blood pressure was recorded from the right carotid artery with a Bell & Howell 4-327-L221 blood pressure transducer connected to a pen recorder. The pulse pressure was differentiated and used as an input signal to a cardiotachometer which in turn was connected to the pen recorder. The left jugular vein was cannulated for intravenous administration of drugs.

Anaesthetized cats with autoperfused hindquarters and a 'delay circuit'

Fifteen cats of either sex, weighing 2 to 3 kg were anaesthetized with pentobarbitone sodium (Nembutal, Abbott), 35 mg/kg intraperitoneally. The trachea and jugular vein were cannulated. Systemic blood pressure was recorded from the right brachial artery and pulse rate was recorded as described above for rats. Respiratory rate was measured by means of a thoracic transducer. The animals were then prepared for perfusion at a constant input volume/min of the whole hindquarters by a method similar to that described earlier (Li & Bentley, 1970a). The abdominal aorta was ligated immediately above the origin of the inferior mesenteric artery. One polyethylene cannula was inserted into the aorta before the point of ligation facing towards the heart and a second cannula was placed immediately beyond the ligature facing caudally. Blood was led from the proximal aorta to the hindlimbs via these cannulae through an H.R. flow inducer pump (Watson-Marlow Ltd., England) and a system interposed between the pump and the animal which delayed the delivery of blood to the hindquarters by 25 to 40 seconds depending upon the pump volume selected. The 'delay system' consisted of a rubber coil of approximately 20 ml capacity filled at the start of the experiment with physiological saline (Bentley & Li, 1968) and immersed in a bath at $40 \pm 0{\cdot}2°$ C. Blood flow to the perfused area was adjusted initially until the perfusion pressure and the systemic blood pressure were approximately equal. Perfusion pressure was measured with a Bell & Howell 4-327 L221 transducer attached to the distal cannula via a T-piece, and was recorded. Changes in the perfusion pressure reflect variation of peripheral resistance in the perfused hindquarters. Coagulation was prevented by intravenous administration of heparin (500 i.u./kg). Noradrenaline 1 μg/kg or depressor drugs (isoprenaline, histamine or acetylcholine each 0·5 μg/kg) were injected into the jugular cannula. Carotid arteries were occluded for 30 s at a time by application of clips. In 2 cats propranolol 250 μg/kg was injected intravenously.

Tolerance studies with rats

Litter mate sibling female rats of the Sprague-Dawley strain weighing 170 to 220 g were used to study the effects of 7 and 14 day treatment with cannabis extract on body weight and daily consumption of food and water. The animals were divided into three groups ; n=the number of rats in a group. Each group received one of the following treatments by intraperitoneal injection (a) Tween 80 (10%) in saline (0·1 ml/100 g)/day for 14 days (n=10), (b) cannabis extract (10 mg/kg)/day for 7 days (n=5), or (c) cannabis extract (50 mg/kg)/day for 14 days (n=10). Water was provided in a graduated feed bottle and the daily consumption recorded when the supply was renewed. Standard mouse-rat diet pellets were supplied daily to the hoppers of Makolon cages in 200 g amounts, when the residue was weighed and discarded. Spillage was observed to be minimal and was ignored. Intake of food was recorded as mean daily consumption per rat. The difference in consumption of rats injected with 10% Tween 80-saline (T) and rats injected with extract of cannabis in Tween 80 solution (C) was expressed as 100 (T−C)/T. Each rat was weighed daily before injection.

One day after the last injection, the animal was anaesthetized with 25% (w/v) urethane. Respiratory rate, systemic blood pressure and pulse rate were recorded as described above. The effects of a single acute dose of cannabis extract (10 mg/kg, i.v.) on the systemic blood pressure, pulse rate and respiratory rate were recorded.

Drugs

The extract of cannabis used in the present studies was Ext. Cannabis Ind. (B.P.C. 1949 suppl. 1952) supplied by Wm. Ransom & Son Ltd. Stock solutions of the extract were prepared by suspending 500 mg in 1 ml of Tween 80 and diluting to 10 ml with distilled water, giving a final concentration of 50 mg/ml. Further dilutions of this stock solution were made as necessary with 0·9% w/v NaCl solution.

The amount of $\triangle^1$-THC present in stock solution of extract of cannabis was assayed by gas liquid chromatography, as descibed by Patterson & Stevens (1970) with the exception that carbon tetrachloride was used as solvent instead of light petroleum. From the results obtained it was calculated that the initial extract of cannabis contained 1·25% of $\triangle^1$-THC.

Stock solutions of $\triangle^1$-THC, $\triangle^6$-THC and cannabinol (imported by Digby Chemical Co. from Makor Chemicals Ltd., Israel) were prepared by suspending the drugs in a concentration of 1 mg/ml in distilled water containing 4% v/v Tween 80. Cannabidiol was dissolved in carbon tetrachloride in a concentration of 100 mg/ml and suspended in 4% Tween 80 to make a final concentration of 1 mg/ml. From these solutions injections were prepared as necessary.

Other drugs used included noradrenaline acid tartrate (Bayer), acetylcholine chloride (Lab. Lamatte et Boinot, 52 Rue La Bruyere, Paris, France), histamine acid phosphate (BDH), atropine sulphate (MacFarlan Smith), pentobarbitone sodium (Abbott), ethyl carbamate (urethane, BDH), isoprenaline sulphate (Burroughs Wellcome), and propranolol hydrochloride (I.C.I.). All doses are expressed in terms of the base.

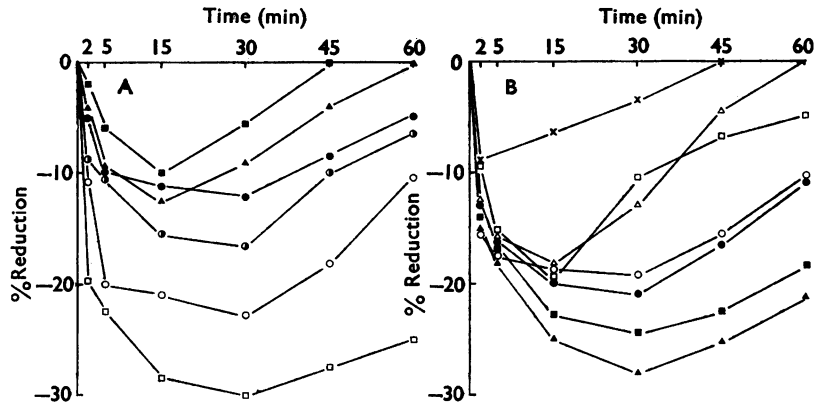

FIG. 1. Rats anaesthetized with urethane. (A) The effects on systemic blood pressure of i.v. administration of (1) Δ^1-THC, 0·5 mg/kg, before (□) and after (■) atropine sulphate 1 mg/kg; (2) extract of cannabis, 1 mg/kg (◑) and 10 mg/kg before (○) and after (●) atropine; (3) Δ^6-THC (▲) 0·5 mg/kg. (B) The effects of Δ^1-THC 0·5 mg/kg (■), extract of cannabis 10 mg/kg (●) and Δ^6-THC 0·5 mg/kg (▲) on respiratory rate: and of the same dose of Δ^1-THC before (□) and after (×) atropine; and of extract of cannabis (○) and Δ^6-THC (△) on the pulse rate. The ordinates are percentage reduction of preinjection levels, abscissae are time in minutes.

Results

Cardiovascular and respiratory effects of extract of cannabis and THC

In rats anaesthetized with urethane, intravenous administration of extract of cannabis (10 mg/kg, $n=16$) or Δ^1-THC (0·5 mg/kg; $n=6$) caused an immediate reduction in pulse rate, a gradual fall in systemic blood pressure (Fig. 1A & B) and a depression of respiratory rate (Fig. 1B). These actions of the extract and of Δ^1-THC persisted for more than 60 minutes. With cannabis extract at 1 mg/kg ($n=3$), only hypotension and bradycardia were observed and respiration was not affected. The degree of hypotension and bradycardia induced by the extract was dose-dependent. Similar cardiovascular and respiratory responses were observed with Δ^6-THC (0·5 mg/kg, i.v., $n=4$) but this THC was less effective than Δ^1-THC in reducing blood pressure and pulse rate (Fig. 1A & B). Neither cannabinol (1 mg/kg, i.v. $n=4$) nor cannabidiol (1 mg/kg, i.v. $n=4$) had an effect on the cardiovascular or respiratory parameters measured. In rats pretreated with atropine sulphate (1 mg/kg i.v.) 10 to 15 min prior to Δ^1THC or extract of cannabis the resulting hypotension and bradycardia were much reduced (Fig. 1A and B). The pretreatment did not have any notable effect on the respiratory changes.

Effects on hindquarter responses

In anaesthetized cats with autoperfused hindquarters, extract of cannabis (10 mg/kg, i.v.) reduced the respiratory rate, systemic blood pressure, pulse rate and hindlimb perfusion pressure (Fig. 2A). This bradycardia was reduced by pre-injection of atropine 1 mg/kg or propranolol 250 μg/kg, but not the systemic hypotension or the fall in perfusion pressure. Chemical assay showed that the Δ^1-THC content of the extract of cannabis was 1·25%; the dosage of Δ^1-THC contained in 10 mg/kg of cannabis extract was therefore 0·125 mg/kg. Pure Δ^1-THC (0·2 mg/kg, i.v.) also depressed the respiratory rate, systemic blood

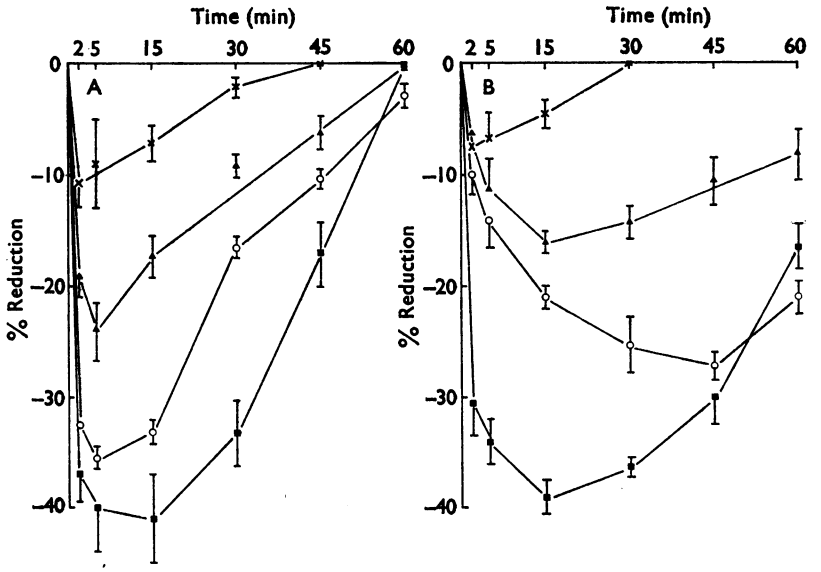

FIG. 2. Autoperfused hindquarters of anaesthetized cats. The effects of i.v. administration of (A) extract of cannabis 10 mg/kg ($\triangle^1$-THC content 0·125 mg/kg) and (B) $\triangle^1$-THC 0·2 mg/kg on respiratory rate (■), systemic blood pressure (○), pulse rate (▲) and hindquarters perfusion pressure (×). The ordinates are percentage reduction of preinjection levels and the abscissae time in minutes.

pressure, pulse rate and hindlimb perfusion pressure in cats (n=5). Figures 2A and B illustrate these effects and indicate that in these doses the two preparations were of approximately equal potency in depressing respiratory rate, pulse rate and perfusion pressure but that the duration of systemic hypotension was longer after administration of $\triangle^1$-THC.

As reported in previous papers (Li & Bentley, 1969, 1970a, 1970b), intravenous administration of noradrenaline (1 μg/kg) evoked a systemic pressor response and a reflex vasodilatation in the hindlimbs, followed by delayed direct vasoconstriction of the hindlimb vasculature when the injected vasoconstrictor substance had traversed the delay circuit. Dilator substances, such as isoprenaline, histamine or acetylcholine, in doses of 0·5 μg/kg, caused systemic hypotension and in the hindquarters reflex vasoconstriction followed by vasodilatation due to the direct action of the drug. These responses were elicited repeatedly in the 15 cats without evidence of tachyphylaxis. This confirms previous reports (Li & Bentley, 1970a, b).

The systemic vasopressor response to intravenously administered noradrenaline (1 μg/kg) was potentiated by extract of cannabis and $\triangle^1$-THC as was the delayed direct vasoconstrictor action on the hindlimb vasculature; and the reflex hindlimb vasodilatation was enhanced (Fig. 3). Propanolol (250 μg/kg), which abolished the depressor response, tachycardia and constrictor reflex after isoprenaline did not abolish the dilator reflex after noradrenaline. Reflex vasoconstriction induced by intravenous injection of histamine (0·5 μg/kg) or acetylcholine (0·5 μg/kg) was markedly reduced by the administration of either extract of cannabis or Δ^1-THC, although the systemic response to these dilator substances was only slightly if at all reduced (Fig. 4) and the direct hindlimb vasodilator response was not significantly altered. The reflex rise in the systemic blood

pressure and the hindlimb perfusion pressure in response to bilateral occlusion for 30 s was also depressed after cannabis extract or Δ^1-THC (Figure 4).

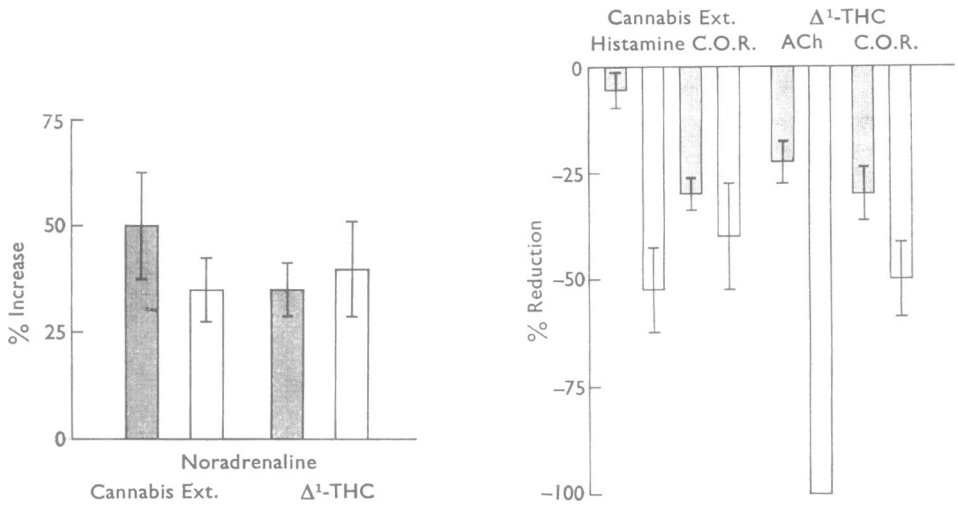

FIG. 3. Autoperfused hindquarters of anaesthetized cats. Effects of i.v. administration of extract of cannabis 10 mg/kg (Δ^1-THC content 0·125 mg/kg) and of Δ^1-THC 0·2 mg/kg on the systemic pressor response (hatched columns) and the reflex vasodilatation in the hindquarters (open columns) after i.v. administration of noradrenaline 1 μg/kg. The mean of 24 observations in 15 cats ± the S.E. of the mean is shown. The ordinate axis is the % increase over the mean of 3 pre-drug responses to noradrenaline in each animal.

FIG. 4. Autoperfused hindquarters of anaesthetized cats. Effects of i.v. administration of (A) extract of cannabis 10 mg/kg (Δ^1-THC content 0·125 mg/kg) on the systemic pressor response (hatched columns) and the reflex vasoconstriction in the hindquarters (open columns) after i.v. administration of histamine 0·5 μg/kg or carotid artery occlusion (C.O.R.) or (B) Δ^1-THC 0·2 mg/kg and acetylcholine (ACh) 0·5 mg/kg or carotid occlusion reflex (C.O.R.). The mean of 24 observations in 13 cats ± the S.E. of the mean is shown. The ordinate axis is the % decrease of the mean of 3 pre-drug responses to histamine or acetylcholine and carotid occlusion in each animal.

Tolerance to the effects of extract of cannabis

(a) Growth curves

The growth curves obtained from three groups of rats are shown in Figure 5. They were treated intraperitoneally with (a) Tween 80—10% in saline, (0·1 ml/100 g)/day for 14 days (n=10), (b) extract of cannabis in 10% Tween 80, (10 mg/kg)/day for 7 days (n=5) and (c) extract of cannabis in 10% Tween 80, (50 mg/kg)/day for 14 days (n=10). The growth rate of rats that were given extract of cannabis (10 mg/kg)/day did not differ significantly from that of the control group. With the high dose of (50 mg/kg)/day, the animals showed an initial drop in food intake (Fig. 5) with a concomitant loss in body weight. Food consumption increased in spite of continuous treatment with the drug and from day 11 onwards the treated animals consumed more food than the controls, accompanied by a considerable recovery of growth. Water consumed by the three groups of rats did not differ significantly in amount.

(b) Cardiovascular and respiratory responses

As shown in Table 1 the blood pressure and pulse rate of rats in groups treated with 10% Tween 80 in saline for 14 days or extract of cannabis (10 mg/kg for

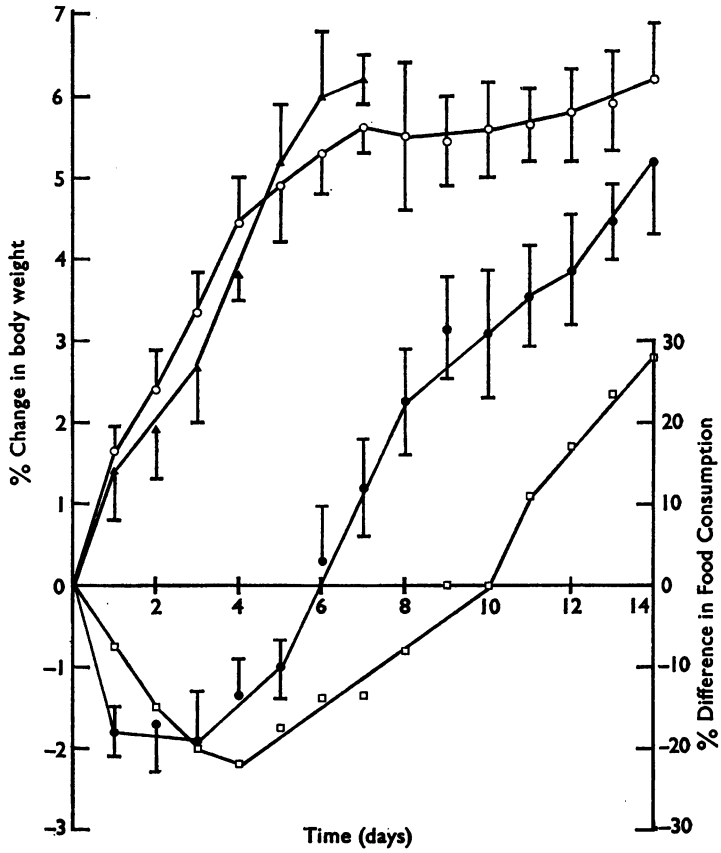

FIG. 5. Growth curves of litter mate female Sprague-Dawley rats injected daily i.p. with (1) 10% Tween 80 in saline, 0·1 ml/100 g. wt for 14 days (○); (2) extract of cannabis 10 mg/kg in solution (1) for 7 days (▲); (3) or 50 mg/kg for 14 days (●). The ordinate axis (left) is the mean change in body wt±S.E. of the mean as a % of initial wt, and the abscissae time in days. Food consumption (□) is shown for group (3). The ordinate axis (right) is the difference in mean daily consumption between groups (3) and (1) as a percentage of (1).

TABLE 1. *The mean systemic blood pressure and pulse rate of urethane anaesthetized rats which had been (a) untreated, (b) treated with* 10% *Tween* 80 *in saline, (c) extract of cannabis in* 10% *Tween* 80 10 *mg/kg)/day for* 7 *days and (d)* (50 *mg/kg)/day for* 14 *days*

Controls n=21		10% Tween 80 in saline for 14 days n=10		Extract of cannabis in 10% Tween 80 (10 mg/kg)/day for 7 days n=5		(50 mg/kg)/day for 14 days n=10	
B.P.±S.E.	P.R.±S.E.	B.P.±S.E.	P.R.±S.E.	B.P.±S.E.	P.R.±S.E.	B.P.±S.E.	P.R.±S.E.
112±4·7	357±27·2	116·7±10·2	346±32·5	106·0±3·7	395·0±12·8	119·7±8·8	380·0±20·6

B.P.=Systemic blood pressure; P.R.=pulse rate; S.E.=standard error of mean; n=the number of rats tested.

7 days or 50 mg/kg for 14 days) and anaesthetized with urethane did not differ significantly from each other or from control rats of the same strain which had not been previously injected. Neither 10% Tween 80 nor extract of cannabis in 10% Tween in the volumes given intraperitoneally caused deterioration of the general condition of the cardiovascular system of these rats. In the rats which had been pretreated with 10% Tween 80 saline for 14 days, intravenous administration of extract of cannabis (10 mg/kg) caused a fall in systemic blood

pressure, pulse and respiratory rates (Figures 6A and B). These effects lasted for more than 60 minutes. The effects of the same dose of extract given intravenously to rats pretreated with extract of cannabis (10 mg/kg)/day for 7 days did not differ significantly from the above (see Fig. 6A for the blood pressure). In animals which had been pretreated with (50 mg/kg)/day for 14 days, intravenous cannabis extract (10 mg/kg) induced a much smaller hypotension (Fig. 6A) and bradycardia and less depression of respiratory rate (Fig. 6B). The degree, rather than the duration, of depression was reduced.

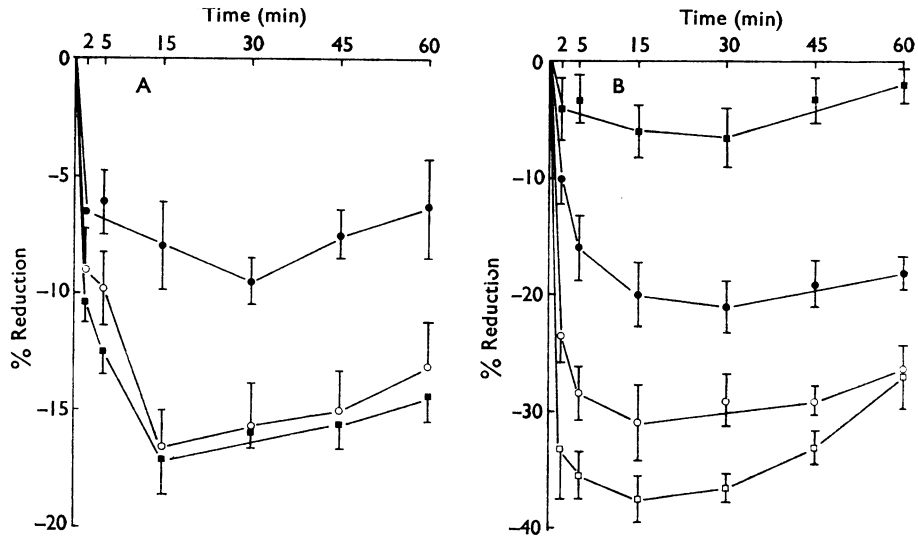

FIG. 6. Rats anaesthetized with urethane; effects of i.v. administration of extract of cannabis 10 mg/kg in 10% Tween 80 (Δ^1-THC content 0·125 mg/kg). (A) systemic blood pressure group (1) 10% Tween 80 in saline 0·1 ml/100 g i.p. daily for 14 days (○); (2) extract of cannabis 10 mg/kg in 10% Tween 80 i.p. daily for 7 days (■); (3) extract of cannabis 50 mg/kg daily i.p. for 14 days ●). (B) Pulse rate group (1) (□); group (3) (■): respiratory rate—group (1) (○); group (3) (●). The ordinates are percentage reductions of pre-injection levels, the abscissae time in minutes.

Discussion

These results confirm that intravenous injection of a suspension of extract of cannabis induces bradycardia, hypotension and slowing of respiratory rate in cats and rats. These effects reach their maximum in 15–30 min and last for more than an hour. Both the magnitude and duration of the responses are dose dependent, and with 1 mg/kg of extract cardiovascular parameters only are depressed, not respiration. Δ^1-THC or Δ^6-THC also produced similar cardiovascular and respiratory depression although Δ^6-THC was less potent than Δ^1-THC in causing hypotension and bradycardia. Δ^1-THC has been regarded as the major psychotomimetically active constituent of cannabis (Hollister, Richards & Gillespie, 1968; Mechoulem, Shani, Edery & Grunfeld, 1970). In the present experiments, cannabinol and cannabidiol had no cardiovascular or respiratory activity when administered alone. Δ^1-THC was probably responsible for the major part of the observed effects of extract of cannabis, with Δ^6-THC contributing.

In the anaesthetized cat with autoperfused hindquarters Δ^1-THC or extract of cannabis caused a fall in hindlimb perfusion pressure, which was not modified

by an effective dose of propranolol, indicating a reduction in vascular resistance in the hindlimb. The systemic hypotensive effect of cannabis cannot be fully explained by this vascular effect since the hindlimb perfusion pressure returned to the control level while systemic blood pressure was still depressed. The curves illustrating depression of pulse rate and systemic blood pressure display similar time relations (Fig. 2A & B) after extract of cannabis and $\triangle^1$-THC but the duration of the depression of these two parameters is significantly longer after 0·2 mg/kg $\triangle^1$-THC than after 10 mg/kg extract of cannabis which contained 0·125 mg/kg $\triangle^1$-THC. This finding supports earlier observations that the initial hypotension was due to a combined reduction in cardiac output and peripheral resistance, but that the prolonged hypotensive effect depended upon a sustained decrease in cardiac output (Cavero & Jandhyala, 1972). We attribute this to a dose dependent cardiac depressant effect of $\triangle^1$-THC, which reduces cardiac contractility in the isolated perfused heart of the rat (Manno, Manno, Kilsheimer & Forney, 1970) and frog (Bose, Saifi & Bhagwat, 1964) and depresses the vasomotor centre of cats (Oskoui, 1972). The antagonism of cannabis-induced bradycardia, by atropine (see Fig. 1) indicates that the reduction in pulse rate is mediated by the vagus nerve. This observation is supported by previous workers who demonstrated the bradycardia caused by $\triangle^1$-THC is central in origin (Cavero & Jandhyala, 1972 ; Milzoff *et al.*, 1971 ; Lahiri, Laddu & Hardman, 1972). The hypotensive effect, therefore, is brought about, at least partly, by a reduction in cardiac output as a consequence of the decrease in pulse rate. Stroke volume has been shown to remain unchanged (Cavero & Jandhyala, 1972).

$\triangle^1$-THC does not interfere with sympathetic ganglionic transmission (Dewey, Yonce, Harris, Reavis, Griffin & Newby, 1970 ; Milzoff *et al.*, 1971) and, therefore, other mechanisms must be sought. Oskoui (1972) reported that $\triangle^1$-THC depressed efferent sympathetic nervous activity while efferent vagal activity was augmented in the cat. The autoperfused hindquarters of the cat have been used to study a wide spectrum of adrenolytic substances. Drugs which interfere with the sympathetic system reduce or block reflex hindlimb vasoconstriction (Li & Bentley, 1970b). Anti-hypertensive drugs, such as guanethidine and reserpine markedly reduced both reflex vasodilatation and vasoconstriction. Moreover, drugs which block the uptake mechanism at adrenergic nerve endings, for example, desmethylimipramine and amphetamine, and clonidine reduced reflex vasodilatation, while reflex constriction was enhanced (Li & Bentley, 1969, 1970a, b).

The ability of extract of cannabis and $\triangle^1$-THC to reduce reflex hindlimb vasoconstriction elicited by either bilateral carotid occlusion or intravenously injected histamine or acetylcholine suggests that THC also exerts an effect via the sympathetic nervous system. This inhibitory action cannot be explained by direct receptor effect because both cannabis extract and $\triangle^1$-THC potentiated the direct delayed vasoconstrictor response to noradrenaline in the perfused hindlimb vasculature and propranolol had no effect on reflex dilatation, or on the fall in perfusion pressure caused by THC. The finding that $\triangle^1$-THC reduced reflex hindlimb vasoconstriction and potentiated reflex vasodilatation suggests that the mechanism by which cannabis affects adrenergic transmission differs from that of other adrenolytic substances.

Behavioural tolerance to $\triangle^1$-THC has been demonstrated in rats, pigeons and chicks after treatment with the drug for periods of 7 days to several weeks

(Bailey *et al.*, 1971 ; Ford & McMillan, 1971 ; Abel, 1972). In rats we found extract of cannabis (10 mg/kg)/day for 7 days, did not affect the cardiovascular and respiratory responses to an acute dose. Furthermore, the treated animals displayed a parallel increase in body weight to the control rats and the food consumptions of the two groups were not statistically different. However, in rats given (50 mg/kg)/day for 14 days, the degree of hypotension, bradycardia and depression of respiratory rate caused by an acute dose of cannabis was markedly reduced. Considerable loss of body weight was also evident in the first few days of the treatment with this dose of the extract and this could be attributed to the reduced food intake during the initial period of treatment. However, food consumption recovered and in the last four days the treated animals consumed more food than the controls. This was accompanied by progressive increase in body wegiht.

It is concluded that tolerance can be induced to the cardiovascular and respiratory effects of extract of cannabis as well as to effects on behaviour.

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