Br. J. Pharmac. (1977), **59**, 561–563

CARDIOVASCULAR EFFECTS OF Δ^9-TETRAHYDROCANNABINOL IN CONSCIOUS AND ANAESTHETIZED DOGS

E. FRIEDMAN, S. GERSHON, B. HINE & MARINA TORRELIO
Department of Psychiatry, New York University School of Medicine, New York, New York 10016, U.S.A.
IMMANUELA RAVE MOSS
Department of Physiology, New York University School of Medicine, New York, New York 10016, U.S.A.

1 Temporal effects of Δ^9-tetrahydrocannabinol (THC) on heart rate and blood pressure in conscious dogs were compared to those in anaesthetized dogs.

3 In conscious dogs, THC in doses of 0.25 and 0.1 mg/kg resulted in maximal heart rate reductions of 48 and 41%, respectively, and in no significant change in blood pressure.

3 In anaesthetized animals THC in doses of 0.5 and 0.25 mg/kg caused a peak reduction in heart rate of 38 and 34%, and of blood pressure of 24 and 8%, respectively.

4 The results demonstrate that the bradycardia in response to THC in dogs is independent of the concomitant anaesthesia.

5 We conclude that the discrepancy between heart rate response to THC in dogs and in man is due to a species difference.

Introduction

Whereas Δ^9-tetrahydrocannabinol (THC) consistently causes tachycardia in man regardless of the route of administration (Hollister, Richards & Gillespie, 1968; Johnson & Domino, 1971; Galanter, Wyatt, Lemberg, Weingartner, Vaughan & Roth, 1972), it is well documented that it causes bradycardia when injected intravenously in anaesthetized dogs (Dewey, Harris, Howers, Kennedy, Granchelli, Pars & Razoan, 1970; Cavero, Kubena, Dziak, Buckley & Jandhyala, 1972; Cavero, Solomon, Buckley & Jandhyala, 1973). Information concerning the cardiovascular effects of THC in conscious dogs is sparse (Dewey *et al.*, 1972; Lahiri, Ladder & Hardman, 1972). The purpose of this study was, therefore, to investigate more fully, in conscious animals, the cardiovascular effects of THC in order to establish whether the discrepant effects of THC in man and dog are due to a species difference or result from the anaesthesia. Such information will clarify the extent to which mechanisms of THC effects in man can be deduced from experiments with dogs.

Methods

Conscious dogs

Three mongrel dogs weighing 12.2 ± 0.6 kg were surgically prepared with exteriorized carotid arteries in skin loops (Gershon & Lang, 1962) for continuous measurements of arterial blood pressure and heart rate. One dog without surgical preparation and weighing 13.5 kg was used for heart rate recording. All dogs were trained to stand in a Pavlov-type harness and accustomed to experimental procedures. Needle-type ECG leads were used for recording Lead II. Heart rate was determined by counting beats/min at the designated times. Control blood pressure and heart rate were measured 20–40 min after the injection of 0.2 ml of ethanol, and were identical to the control values obtained before ethanol. These control measurements were immediately followed by an intravenous injection of THC (0.1 or 0.25 mg/kg) dissolved in the same volume of ethanol. Behaviour was observed before and for 70 min following drug administration. In a single animal the two doses of THC were administered 2–3 weeks apart in random order.

Anaesthetized dogs

Male mongrel dogs weighing 17.3 ± 0.2 kg were lightly anaesthetized with intravenously administered sodium pentobarbitone (25 mg/kg). Rectal temperature was maintained at 38 ± 0.5°C. A femoral venous catheter was used for drug injection and a femoral arterial catheter for measurements of arterial pressure and

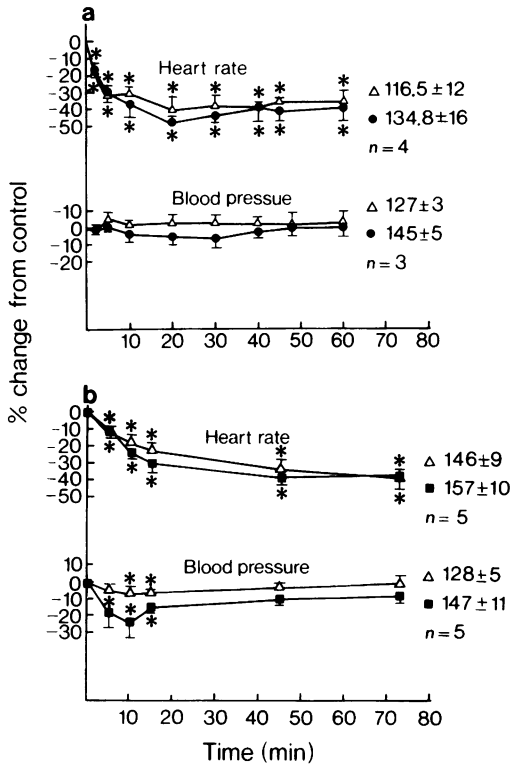

Figure 1 Temporal effects of intravenous administration (a) of 0.25 (●) and 0.10 mg/kg (△) Δ^9-tetrahydrocannabinol in awake dogs, and (b) of 0.50 (■) and 0.25 mg/kg (△) Δ^9-tetrahydrocannabinol in anaesthetized dogs, on heart rate and mean arterial blood pressure. Percentage changes from control are indicated on the ordinate scale. Each point and vertical line represents the mean ± s.e. mean.

* Significant change from control ($P < 0.05$ by Student's t test).

Mean control values ± s.e. mean are shown on the right-hand side for each parameter.

heart rate. Needle-type ECG leads were used for recording Lead II. THC (0.25 and 0.5 mg/kg) and cannabidiol (CBD, 0.5 mg/kg) were dissolved in ethanol (0.25 ml) for injection.

Results

Conscious dogs

Control values of heart rate and mean arterial pressure, and the effect of THC (0.25 and 0.10 mg/kg) on these two functions in conscious dogs are depicted in Figure 1. A precipitous fall in heart rate occurred during the initial 5 min (30% of control) following both doses of THC. Heart rate reached minimum (41–48% of control) 20 min after THC injection and remained at that level for 60 minutes. The degree of bradycardia in response to THC was not dose-related. Bradycardia was associated with sinus arrhythmia in both conscious and anaesthetized dogs. Mean arterial blood pressure in response to THC was not different from control.

Rear leg ataxis, front leg rigidity and sagging back appeared as early as 5 min after THC injection, and was dose-related. Hyper-reactivity to touch and sound occurred approximately 10 min after drug injection, and lasted throughout the experiment. Spontaneous jerks and intermittent head-drops ('nodding') were clearly observed 5 to 40 min after drug injection in 6 out of 8 experiments performed. Mydriasis, conjunctival injection and leg tremor were also observed.

Anaesthetized dogs

The effects of 0.5 and 0.25 mg/kg THC on heart rate and mean arterial blood pressure, calculated in terms of percentage change from control, are summarized in Figure 1. Heart rate diminished rapidly during the first 15 min and was at a minimum 45 and 75 min after both doses of THC. No statistically significant difference between the two doses was observed.

Hypotension was mild and reached its peak 10 min after drug injection. This effect was dose-related, in that blood pressure decreased by 8% with 0.25 mg/kg and by 24% with 0.5 mg/kg of THC.

An intravenous injection of cannabidiol (0.5 mg/kg) in 3 dogs resulted in no alteration in heart rate or in mean arterial blood pressure during 45 min of observation.

Discussion

The significance of the present study lies in the fact that the cardiovascular effects of THC were compared in both conscious and anaesthetized animals. Moreover, the cardiovascular measurements in conscious animals were made intra-arterially, thus minimizing the effect of stress inherent in other measurement techniques (Dewey *et al.*, 1972). The doses employed in our conscious dog experiments were within the range of those used by marijuana smokers.

The effect of THC on blood pressure in human subjects is variable. Our findings that 0.5 mg/kg THC induces a transient hypotension in anaesthetized dogs, and 0.1 and 0.25 mg/kg of THC produce no blood pressure changes in conscious dogs, confirm previous studies in anaesthetized dogs (Cavero *et al.*, 1973) and extend those in conscious dogs in which much higher doses of THC were employed (Dewey *et al.*, 1972;

Lahiri *et al.*, 1972). The discrepancy in blood pressure responses between conscious and anaesthetized animals might be attributed to the lack of compensatory vascular reflexes in the anaesthetized preparation.

Previous results on the effects of THC on heart rate in anaesthetized animals (Dewey *et al.*, 1970; Cavero *et al.*, 1972) stand in contrast to those in human subjects (Perez-Reyes, Timmons, Lipton, Davies & Wall, 1972; Galanter *et al.*, 1972; Johnson & Domino, 1972), and could have been attributed in part to an interaction of THC with anaesthetics. The present finding of bradycardia in both anaesthetized and conscious dogs dispels this notion. This difference may stem, at least in part, from the marijuana-induced 'high' in human subjects.

While this possibility is supported by the finding that human subjects developed both psychological tolerance as well as bradycardia in response to chronic THC (Benowitz & Jones, 1975), the lack of temporal correlation between the euphoria and bradycardia (Gallanter *et al.*, 1972) makes this explanation less likely. It is, therefore, concluded that the discrepancy in heart rate response to THC in man and dog is due to a species difference. Furthermore, one should exercise caution in deducing that the cardiovascular mechanism involved in THC effects in experiments on dogs apply to man.

References

BENOWITZ, N.L. & JONES, R.T. (1975). Cardiovascular effects of prolonged delta-9-tetrahydrocannabinol ingestion. *Clinical Pharmac. Ther.*, **18**, 287–297.

CAVERO, I., KUBENA, R.K., DZIAK, J., BUCKLEY, J.P. & JANDHYALA, B.S. (1972). Certain observations on interrelationships between respiratory and cardiovascular effects of (–)-Δ^9-trans-tetrahydrocannabinol. *Res. Commun. Chem. Pathol. Pharmac.*, **3**, 483–492.

CAVERO, I., SOLOMON, T., BUCKLEY, J.P. & JANDHYALA, B.S. (1973). Studies on the bradycardia induced by (–)-Δ^9-trans-tetrahydrocannabinol in anesthetized dogs. *Eur. J. Pharmac.*, **22**, 263–269.

DEWEY, W.L., JENKINS, J., O'ROURKE, T. & HARRIS, L.S. (1972). The effects of chronic administration of trans-Δ^9-tetrahydrocannabinol on behavior and the cardiovascular system of dogs. *Archs int. Pharmacodyn.*, **198**, 118–131.

DEWEY, W.L., HARRIS, L.S., HOWES, J.F., KENNEDY, J.S., GRANCHELLI, F.E., PARS, H.O. & RAZOAN, R.J. (1970). Pharmacology of some marijuana constituents and two heterocyclic analogues. *Nature, Lond.*, **226**, 1265.

GALANTER, M., WYATT, R.J., LEMBERG, L., WEINGARTNER, H., VAUGHAN, T.B. & ROTH, W.T. (1972). Effects on humans of Δ^9-tetrahydrocannabinol administered by smoking. *Science, N.Y.*, **175**, 934–963.

GERSHON, S. & LANG, W.J. (1962). A psychopharmacological study of some indole alkaloids. *Archs int. Pharmacodyn.*, **135**, 31–56.

HOLLISTER, L.E., RICHARDS, R.K. & GILLESPIE, H.K. (1968). Comparison of tetrahydrocannabinol and synhexyl in man. *Clin. Pharmac. Ther.*, **9**, 783–791.

JOHNSON, S. & DOMINO, E.F. (1972). Some cardiovascular effects of marijuana smoking in normal volunteers. *Clin. Pharmac. Ther.*, **12**, 762–768.

LAHIRI, P.K., LADDER, A.R. & HARDMAN, H.F. (1972). Effects of tetrahydrocannabinol (THC) on the heart rate of the dog. *Fedn Proc.*, **31**, 1646.

PEREZ-REYES, M., TIMMONS, M.C., LIPTON, M.A., DAVIS, K.H. & WALL, M.E. (1972). Intravenous injection in man of Δ^9-tetrahydrocannabinol and 11-OH-Δ^9-tetrahydrocannabinol. *Science, N.Y.*, **177**, 633–634.

(Received July 12, 1976. Revised September 28, 1976.)