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Cannabinoids. II. Cardiovascular Effects[1]

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ABSTRACT

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The cardiovascular effects of two new cannabinoids, nabilone and canbisol, have been compared to Δ^9-tetrahydrocannabinol (Δ^9-THC) and chlordiazepoxide. Unanesthetized rabbits, dogs, hypertensive rats and rhesus monkeys have been studied. In rabbits, modest falls in blood pressure and heart rate were produced by 0.05 mg/kg of Δ^9-THC, 0.064 mg/kg of nabilone and 0.001 mg/kg of canbisol, all i.v. Chlordiazepoxide had no effect up to 0.50 mg/kg. In dogs, i.v. Δ^9-THC caused no cardiovascular changes up to 0.25 mg/kg, and chlordiazepoxide had no effect up to 10 mg/kg. Nabilone caused a modest delayed increase in blood pressure at 0.064 mg/kg and canbisol a modest hypotension at 0.004 mg/kg, an effect not intensified at hyperdoses. Repeated daily oral administration of canbisol, 0.16 mg/kg, to hypertensive rats led to a fall of 30 mm Hg that was as large after the sixth dose as after the first. In rhesus monkeys, 0.1 mg/kg of Δ^9-THC, 0.01 mg/kg of nabilone and 0.003 mg/kg of canbisol i.v. caused modest falls in blood pressure with little consistent change in heart rate. Very large doses of Δ^9-THC, nabilone and canbisol produced sustained hypotension interrupted by dramatic periods of hypertension. The hypotensive effects of canbisol did not reduce the pressor effect of *l*-norepinephrine and the hypotension was overcome by vigorous exercise. Chlordiazepoxide caused no cardiovascular effects until massive doses (30 and 100 mg/kg) were given and then the effects were an increase in blood pressure. We conclude that a major contribution to the cardiovascular effects of cannabinoids is exerted through their behavioral effects with consequences on skeletal muscle activity. The variability in the cardiovascular effects according to circumstances derives from dependence of the behavioral effects on environmental circumstances.

Study of the cardiovascular (CV) effects of cannabinoids has been complicated by a number of factors. First, until the recent identification of Δ^9-tetrahydrocannabinol (Δ^9-THC) as the main active ingredient of marijuana, there was no standard comparison compound, so attention was spread over many compounds as well as species and preparations, making systematic comparisons difficult. Second, there are many indications that the CV effects of cannabinoids are greatly affected by the presence and type of anesthesia (see, for example, Friedman et al., 1977). Third, the CV effects of the drugs seem to vary depending on the functional state of the CV system, and so the effects of the same dose of the same drug may vary from time to time. In the course of the present work yet another reason for the difficulty in understanding the CV effects of cannabinoids has been noted: the dose-effect curve may be non-monotonic.

As in the previous paper, interest in two new cannabinoids has led to reconsideration of the CV effects of Δ^9-THC and also of chlordiazepoxide. The new cannabinoids, nabilone and canbisol, and some aspects of their behavioral pharmacology are described in the previous paper (Stark and Dews, 1980). In the present work, CV effects in rabbits, dogs, hypertensive rats and rhesus monkeys have been studied in unanesthetized subjects and comparisons of the four compounds, Δ^9-THC, chlordiazepoxide, nabilone and canbisol have been made.

It has been reported that Δ^9-THC in the unanesthetized dog causes a substantial fall in heart rate (HR), not related to dose from 0.10 to 0.25 mg/kg i.v., and without change in blood pressure (BP) (Friedman *et al.*, 1977); earlier workers had found a fall in BP with 0.3 mg/kg i.v. (Dewey *et al.*, 1970). In humans, however, following Δ^9-THC either i.v. or p.o. there is an increase in HR (Perez-Reyes *et al.*, 1972, 1973). Hollister *et al* (1968) reported slightly reduced systolic and diastolic BP and increased HR after Δ^9-THC, and these findings have been widely quoted. They gave 16 subjects a median dose of 0.58 mg/kg (range 0.34–0.95 mg/kg) of Δ^9-THC by mouth. The average systolic BP went from 119 mm Hg before drug to 120 mm Hg at 2 hr, 110 at 4 hr and 113 at 7 hr. The corresponding figures for diastolic BP were 77, 73, 71 and 68 and for HR 65, 84, 82 and 86. The effects on BP were thus slight, as reported, with the effect on diastolic, but not systolic, being greater at 7 than at 4 hr. The effects on HR were more substantial, but again, the greater effect at 7 than at 4 hr, and the absence of controls makes the significance of even these substantial doses difficult to assess. Even when coma was produced by presumptive overdosage with marihuana, BP fell only to 80/50 and HR was 100 (Beaconsfield *et al.*, 1974).

There appear to be no reports on the CV effects of chlordi-

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azepoxide in unanesthetized animals. In anesthetized dogs, chlordiazepoxide at 4 mg/kg i.v. caused a fall in both BP and HR (Daniell, 1975).

Methods

BP and HR of rabbits. Male white rabbits weighting 2.5 to 3.5 kg were given permanent arterial cannulas. Under secobarbital (30 mg/kg i.v.) anesthesia the abdomen was opened and a Tygon cannula was inserted into the aorta at its bifurcation and advanced to just distal to the renal artery. The distal end of the cannula was looped, anchored to the posterior abdominal wall, then passed through the muscle layers, run subcutaneously rostrally and exited at the nape of the neck. Between recording sessions, the cannula was filled with heparin (100 units/ml) and plugged with a stylet. During recording, heparin 50 units/ml in deionized water was infused through the transducer (Statham) and the cannula at the rate of 0.01 ml/min by a continuous infusion pump (Harvard Apparatus Co., Millis, MA). Mean arterial BP, obtained by electrical damping, and HR were recorded on a polygraph (Grass Instruments Co., Quincy, MA) and from thence into a computer. The rabbit was placed in a stock and 30 min later a 30 min control period of recording started. Drug was then administered into an ear vein and recording continued for 120 min. Mean arterial BP and HR values at 10-min intervals were averaged over the 120-min period following drug.

BP, HR and electrocardiogram of dogs. Male dogs were prepared with permanent venous and arterial cannulas. The cannulas were introduced into the inferior vena cava and into the aorta via the circumflex iliac vein and artery, so the tips were distal to the renal vessels. The cannulas were anchored, exteriorized and filled, as in the rabbit described above. Infusion during recording was at the rate of 0.0025 ml/min. The dog was confined to a chamber but otherwise not restrained. The transducer was mounted adjacent to the point where the arterial cannula emerged from the dog and the leads carried by movable cable to a swivel (Lehigh Valley Electronics, Fogelsville, PA) and so to the polygraph. Two electrodes were attached to the dog in ECG lead II position and the leads from them also brought through the swivel to the polygraph for periods of ECG recording.

After a control period of recording of at least 30 min, drugs were given either i.v. via the venous cannula or by mouth and recording continued at least for a further 90 min. BP and HR values at 30, 60, and 90 min after drug were tabulated except for observations on Δ^9-THC at 0.20 and 0.25 mg/kg i.v. when only the first 30 min after the drug were recorded. Measurements of ECG at the same intervals were similarly averaged.

BP of hypertensive rats. Spontaneously hypertensive male rats of the Okamoto-Aoki strain (Wistar derived) had their BP measured by the rail cuff method. After 5 min in a warming box at 31°C the rats were put in a holder. A cuff was attached to the tail and inflated at a steady rate. Pulsations from the tail were transmitted to a transducer and recorded on a physiograph. Recordings were made before oral dosing and again 2 hr later. Only canbisol was studied in rats.

BP and HR of rhesus monkeys. Male rhesus monkeys were prepared as previously described (Dews and Herd, 1974); the procedure was identical to that described for dogs except that the arterial cannula was introduced via the internal iliac artery and the venous cannula via the external iliac vein. For recording, the monkey was confined in a primate restraining chair in a sound attenuating chamber. The transducer was mounted on the outside of the chamber. After a control period of at least 30 min, drugs were given either i.v. through the venous cannula or i.m. deep into the gastrocnemius-soleus and recording continued at least a further 90 min with BP and HR tabulated for 30, 60 and 90 min after drug. Doses were spaced at least 2 weeks apart and for the larger doses at least a month apart.

Additional experiments were made in which *l*-norepinephrine was introduced through the venous cannulas as a rapid injection of 0.025

TABLE 1

Effects of nabilone, canbisol, Δ^9-THC and chlordiazepoxide in unanesthetized rabbits on mean arterial blood pressure and heart rate predrug (0) and at 30, 60 and 90 min after drug

Dose	Route	N*	BP				HR			
			0	30	60	90	0	30	60	90
			mm Hg				beats/min			
Vehicle	i.v.	71	91	86	86	87	228	244	246	250
mg/kg										
Nabilone										
0.008	i.v.	4	83	74*	74*	80	199	202	201	199
0.016	i.v.	4	88	84	89	73	246	257	250	232
0.032	i.v.	4	88	84	89	73	260	248	237*	222*
0.064	i.v.	5	75	58*	57*	56*	163	136*	128*	121*
0.125	i.v.	4	85	68*	68*	65*	172	167	158	172
Canbisol										
0.00025	i.v.	4	83	78	78	78	230	230	226	221
0.005	i.v.	4	82	72	79		176	160	165	
0.001	i.v.	13	81	65*	64*	67*	204	196	184*	215
0.002	i.v.	32	87	71*	72*	72*	209	196	192	197
0.004	i.v.	12	88	67*	66*	69*	220	201	181*	176*
0.008	i.v.	18	87	69*	67*	69*	194	177	167*	168*
0.016	i.v.	4	107	97	97	93	230	276*	271*	275*
Δ^9-THC										
0.025	i.v.	4	80	71*	76	81	225	224	223	228
0.05	i.v.	4	89	67*	74*	70*	238	214*	248	272
0.10	i.v.	4	69	59*	56*	61*	248	205*	202*	230
0.20	i.v.	4	81	70	73	75	240	224	220	229
Chlordiazepoxide										
0.063	i.v.	4	73	73	70	72	206	215	218	222
0.125	i.v.	4	83	77	76	84	207	250	248	253
0.25	i.v.	4	85	77	73	77	207	237	248	259
0.5	i.v.	4	86	81	78	78	192	241	234	233

* *N* = number of observations.
* Significantly different from control ($P < .05$).

mg every 5.5 min. Finally, the monkeys were trained to exert a vertical downward pull of at least 6 kg of an inverted T-bar, as described by Dews and Herd (1974). Brief pulls of this force occurred every 3 to 4 sec for periods of 5 min followed by rest periods of 15 min.

Drugs. Cannabinoids were given orally to rats and dogs as a suspension in 1% Tween 80 at 4 ml/kg. For intravenous administration the cannabinoids were dissolved in ethanol, and the solution was diluted with 0.05% Tween 80 to give a final ethanol concentration of 5%. The dose was contained in 0.2 ml/kg.

Chlordiazepoxide was given as the aqueous solution of the hydrochloride. *l*-Norepinephrine bitartrate was dissolved in 0.1 N HCl and diluted for injection. Doses are given in terms of base.

Statistics. Statistical significance was assessed by Student's *t* test comparisons of control values with values after individual doses of the drugs.

Results

Effects in rabbits. A modest fall in BP followed as little as 0.05 mg/kg of Δ^9-THC, but the effect did not increase recognizably at 0.10 and 0.20 mg/kg and even appeared to be less at 0.20 mg/kg (table 1). There was an accompanying modest fall in HR. Chlordiazepoxide had equivocal effects at doses up to 0.50 mg/kg (table 1). Nabilone had no convincing effect until a dose of 0.064 mg/kg was reached when there was a substantial fall in both BP and HR. The BP but not the HR fell after 0.125 mg/kg (table 1). Canbisol had similar effects starting with as little as 0.001 mg/kg, and again, the fall in BP was accompanied by a fall in HR (table 1). The highest dose studied, 0.016 mg/kg, however, caused no fall in BP and a significant *increase* in HR. The doses of 0.125 mg/kg of nabilone or 0.016 mg/kg of canbisol, which no longer produced a fall in HR, caused sprawling of the hind legs and immobility.

Repeated daily administration i.v. of a small dose of canbisol (0.008 mg/kg) for 5 days lowered the BP to about 60 mm Hg whether the mean predrug pressure was 93 mm Hg (as on day 0) or only 77 mm Hg (as on day 4) (table 2). There was no indication of development of tolerance at this dose level, the

TABLE 2

Effect of repeated daily injections of canbisol on BP of four rabbits

Day	Dose	BP	
		0 min	Min[a]
	mg/kg i.v.	*mm Hg*	
0	0.008	93 ± 4.4[b]	65 ± 5.5[b]
1	0.008	73 ± 3.0	57 ± 3.9
2	0.008	78 ± 2.7	59 ± 5.0
3	0.008	79 ± 6.1	58 ± 4.2
4	0.008	77 ± 2.1	61 ± 3.9
5	Vehicle	78 ± 6.8	73 ± 5.9
6	Vehicle	78 ± 2.7	73 ± 3.2
7	Vehicle	77 ± 4.7	75 ± 4.9

[a] Minimum level of BP observed during repeated measurements over a 2-hr period after drug.
[b] Mean ± S.E.

TABLE 4

Effects of nabilone on some features of ECG of unanesthetized dogs predrug (0) and at 30, 60 and 90 min after drug

Dose	Interval	0	30	60	90
mg/kg i.v.					
0.031	PR	0.14	0.14	0.14	0.14
	QRS	0.08	0.06	0.06	0.06
	QT	0.34	0.36	0.34	0.35
	RR	0.92	1.41	1.15	0.99
	QT/RR	0.35	0.30	0.32	0.35
0.13	PR	0.12	0.10	0.10	
	QRS	0.07	0.06	0.06	
	QT	0.26	0.25	0.26	
	RR	0.92	0.92	0.86	
	QT/RR	0.27	0.27	0.26	

TABLE 3

Effects of nabilone, canbisol, Δ^9-THC and chlordiazepoxide in unanesthetized dogs on BP and HR predrug (0) and at 30, 60 and 90 min after drug

Dose	Route	N[a]	BP				HR			
			0	30	60	90	0	30	60	90
mg/kg			*mm Hg*				*beats/min*			
Vehicle	i.v.	6	110 ± 8.5[b]	115 ± 8.3[b]	110 ± 7.9[b]	115 ± 14.6[b]	95 ± 10.5[b]	95 ± 19.1[b]	86 ± 14.4[b]	91 ± 18.8[b]
Vehicle	p.o.	4	102 ± 7.3[b]	102 ± 6.7[b]	101 ± 2.9[b]	96 ± 6.2[b]	94 ± 14.2[b]	88 ± 11.9[b]	93 ± 14.6[b]	84 ± 26.9[b]
Nabilone										
0.008	i.v.	3	82	73	83	88	72	72	81	80
0.032	i.v.	7	94	94	89*	88	68	50	58	59
0.064	i.v.	1	100	90	150*		80	60	92	
0.13	i.v.	3	97	115	105	132	69	80	89	113
1.25	p.o.	1	114	115	109	114	134	170*	164*	88
2.5	p.o.	1	110	90	100	122	100	67	64	88
Canbisol										
0.001	i.v.	3	88	85	88	85	84	84	80	80
0.002	i.v.	14	107	109	104	109	73	73	76	79
0.004	i.v.	8	99	94	89*	94	78	68	71	74
0.008	i.v.	7	95	90	86*	91	77	78	83	85
0.016	i.v.	2	95	98	88*	88	68	78	82	82
0.032	i.v.	1	75*	75*	65*	70*	80	88	100	100
0.064	i.v.	2	88*	88*	88*	90	78	80	90	104
Δ^9-THC										
0.125	i.v.	2	113	113	127*		81	74	84	
0.20	i.v.	1	90	100			64	104		
0.25	i.v.	2	108	105			55	59		
Chlordiazepoxide										
5.0	i.v.	2	116	116	116	125	104	108	98	112
10.0	i.v.	2	112	110	108	106	80	159*	143	148*

[a] *N* = number of observations.
[b] Mean ± S.D.
* Significantly different from control ($P < .05$).

minimum pressure being the same after the second through the fifth doses.

Effect in dogs. Δ^9-THC caused no convincing change in BP or HR in doses up to 0.25 mg/kg i.v., the highest dose studied, at least in the first ½ hour after administration (table 3). Chlordiazepoxide showed no effect on BP up to 10 mg/kg i.v. but an increase in HR at that dose. Nabilone caused no clear effects at lower doses, but there is an indication of a delayed increase in BP following 0.064 and 0.13 mg/kg i.v. Canbisol produced some slight hypotension at 0.004 mg/kg i.v., but the effect was not intensified at higher doses.

The only change detected in the ECG was the inevitable increase in RR interval when the HR fell after 0.032 mg/kg (table 4).

Repeated daily administration i.v. of a small dose of canbisol (0.008 mg/kg) for 4 days appeared to cause a modest sustained fall in BP and HR that partly recovered in 2 days when dosing was discontinued (table 5).

Effects in hypertensive rats. The effects of repeated daily administration p.o. of increasing doses of canbisol up to 0.16

TABLE 5

Effects of repeated daily injections of canbisol on mean BP and HR of two dogs predrug (0) and 60 min after drug (60)

Day	Dose	BP		HR	
		0	60	0	60
	mg/kg i.v.	mm Hg		beats/min	
1	0.008	102	108	72	78
2	0.008	92	98	52	52
3	0.008	88	88	46	54
4	0.008	88	90	50	54
5	Vehicle	88	75	56	56
6	Vehicle	95	100	60	62

TABLE 6

Effects of repeated daily injections of canbisol on mean BP of 12 hypertensive rats predrug (0) and 120 min after drug (120)

Day	Dose	BP	
		0	120
	mg/kg p.o.	mm Hg	
0	Vehicle	201 ± 4.7[a]	196 ± 4.7[a]
1	Vehicle	200 ± 5.1	195 ± 3.3
2	0.04	187 ± 2.6	186 ± 4.6
3	0.08	194 ± 3.1	191 ± 4.4
4	0.16	197 ± 3.3	168 ± 3.6
5	0.16	189 ± 3.0	166 ± 3.0
6	0.16	189 ± 5.8	161 ± 5.2
7	0.16	190 ± 3.6	190 ± 9.4
8	0.16	182 ± 5.4	165 ±5.7
9	0.16	173 ± 6.6	143 ± 7.5
10	Vehicle	183 ± 5.2	193 ± 3.2
11	Vehicle	186 ± 4.3	189 ± 7.4

TABLE 7

Effects of nabilone, canbisol, Δ^9-THC and chlordiazepoxide on BP and HR of unanesthetized rhesus monkeys predrug (0) and at 30, 60 and 90 min after drugs

Dose	Route	N[a]	BP				HR			
			0	30	60	90	0	30	60	90
mg/kg			mm Hg				beats/min			
0		18	96 ± 2.6[b]	96 ± 2.7[b]	93 ± 2.9[b]	90 ± 2.0[b]	149 ± 8.1[b]	148 ± 6.7[b]	146 ± 6.2[b]	147 ± 6.5[b]
Nabilone										
0.01	i.v.	2	100	82	78*	88	130	110	105	100
0.03	i.v.	4	92	76*	75*	76*	132	132	128	125
0.10	i.v.	4	94	75*	76*	81	118	115	109	112
0.30	i.v.	2	98	90	70*	65*	135	145	125	120
0.30	i.m.	2	102	92	88	88	125	165	120	120
1.0	i.v.	4	90	55*	55*	55*	140	148	148	135
1.0	i.m.	2	128	125	120	115	140	145	155	155
3.0	i.m.	2	114	138*	120	125	140	210*	185	180
Canbisol										
0.003	i.v.	3	102	88*	86*	89*	155	158	162	153
0.007	i.v.	7	101	76*	75*	79*	151	137	127	123
0.01	i.v.	7	100	66*	74*	74*	160	151	144	139
0.03	i.v.	8	95	56*	61*	62*	142	148	141	139
0.03	i.m.	2	108	95	95	98	140	145	145	135
0.10	i.v.	2	105	50*	80*	85*	160	145	155	160
10.00	i.m.	1	115	45*	50*	50*	220	170	160	140
Δ^9-THC										
0.01	i.v.	1	80	80	110	100	100	80	140	120
0.03	i.m.	1	95	95	95	95	160	150	150	150
0.10	i.v.	5	92	78*	84*	99*	174	166	168	176
0.30	i.v.	2	105	108	102	100	200	200	200	185
0.30	i.m.	2	92	95	92	90	130	160	150	145
1.00	i.v.	4	95	107	100	105	167	183	170	167
1.00	i.m.	3	101	110	113	103	146	157	173	157
3.00	i.v.	1	105	35*	40*	50*	210	160	170	180
Chlordiazepoxide										
3.0	i.m.	4	96	99	98	100	150	168	165	165
10.0	i.m.	7	88	89	89	88	149	153	153	156
30.0	i.v.	2	90	90	105	102	160	155	180	185
30.0	i.m.	6	100	114*	118*	113*	152	180	178	180
100.0	i.v.	2	90	112*	125*	112*	110	150	165	160

[a] N = number of observations.
[b] Mean ± S.E.
* Significantly different from control ($P < .05$).

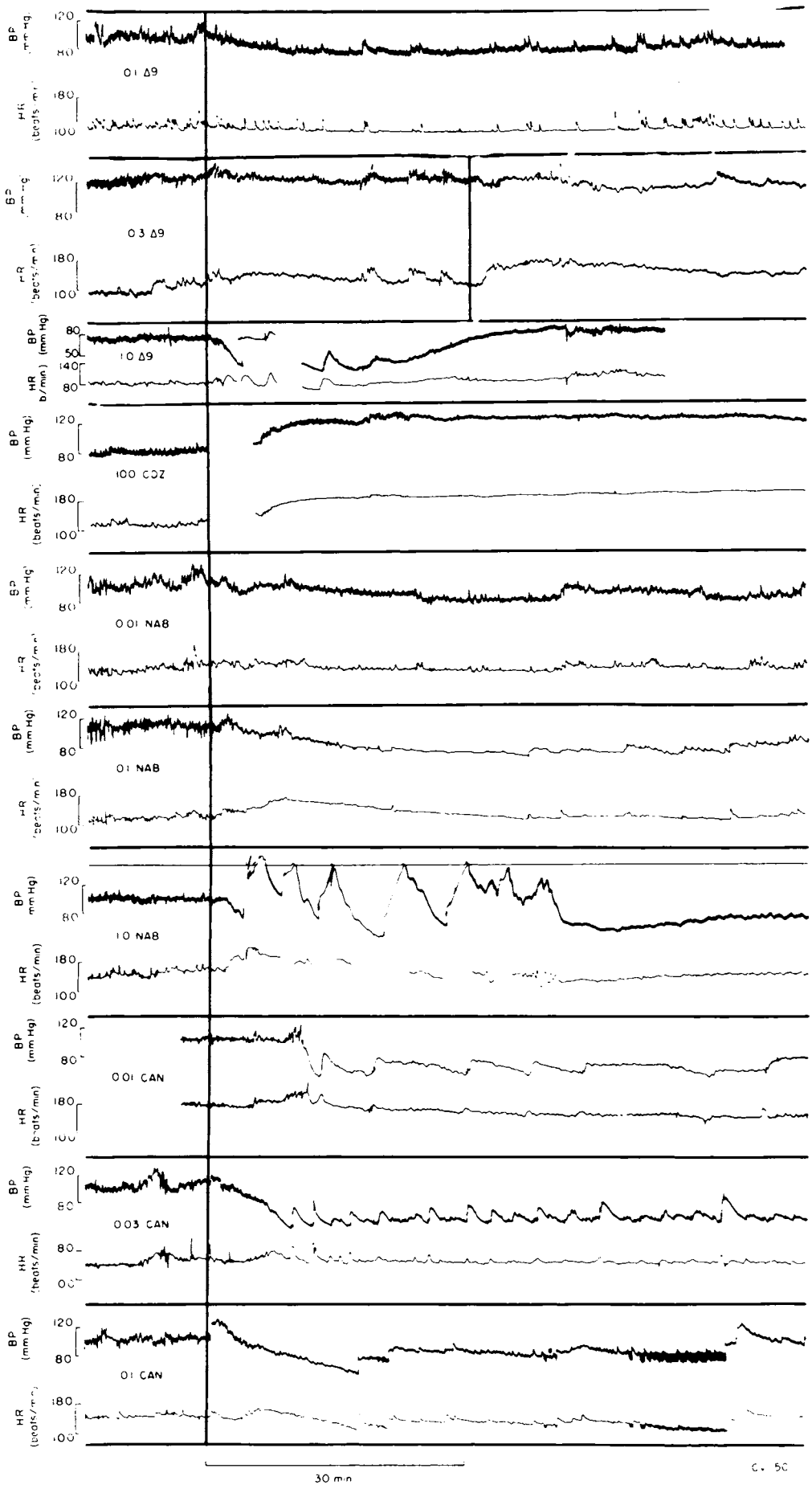

Fig. 1. CV effects of i.v. injection of cannabinoids and chlordiazepoxide in an unanesthetized rhesus monkey. Each row shows BP above and HR below, scales as indicated. Doses were given at the vertical black line except in second row where 5 ml of 1% Tween 80 was given at first vertical line and the dose of drug at the second. Tween 80 at 20 times the dose used to suspend the cannabinoids had no effect. From above: 0.1 Δ^9 (0.1 mg/kg of Δ^9-THC) caused a slight sustained fall in BP with no change in HR except a reduction in fluctuations of rate. 0.3 Δ^9 (0.3 mg/kg of Δ^9-THC) caused a less clear fall in BP than 0.1 mg/kg and an increase in HR. 1.0 Δ^9 (1.0 mg/kg of Δ^9-THC) caused a large fall in BP to less than 50 mm Hg followed by a brief period of recovery then a long period of hypotension. The 5 to 10 min of recovery show that the hypotensive effects of Δ^9-THC are physiologically surmountable. HR showed no sustained change. 100 CDZ (100 mg/kg of chlordiazepoxide) caused substantial and sustained increases in both BP and HR. 0.01 NAB (0.01 mg/kg of nabilone) caused a just recognizable but sustained fall in BP with no change in HR. 0.1 NAB (0.1 mg/kg of nabilone) caused a clear, sustained hypotension accompanied initially by an increase in HR. 1.0 NAB (1.0 mg/kg of nabilone) caused prolonged, profound hypotension interrupted by long paroxysms of hypertension. The hypotensive effects of nabilone were clearly physiologically surmountable. HR was initially increased. 0.01 CAN (0.01 mg/kg of canbisol) caused effects similar to but somewhat greater than 0.03 mg/kg of nabilone, q.v. 0.03 CAN (0.03 mg/kg of canbisol) caused sustained hypotension with brief partial recoveries and little change in HR. 0.1 CAN (0.1 mg/kg of canbisol) caused prolonged hypotension, initially profound, and a general decline in HR.

mg/kg, and then six doses of 0.16 mg/kg were studied (table 6). The 0.04 and 0.08 mg/kg doses were without effect, but the 0.16 mg/kg dose led to a fall in BP of about 30 mm Hg that was as large after the sixth dose as after the first dose.

Effects in monkeys. No clear effect was seen with Δ^9-THC i.v. in doses below 0.1 mg/kg, but this dose caused a modest and short-lived (about 1 hr) fall in BP, with little change in HR (table 7; fig. 1). The fall in BP was not seen with the dose of 0.3 mg/kg i.v. The effects were variable following 1.0 mg/kg i.v. Sometimes (one out of four observations) there was a marked fall in BP (illustrated in fig. 1), but more often (three out of four observations) there was a modest rise. Effects were seen following i.m. injection only at 1 mg/kg and the effect was a modest rise of BP. A dose of 3 mg/kg i.v. in a single observation caused a catastrophic fall in BP with paroxysms of hypertension and little change in HR, similar to the effects illustrated in figure 1 following 1.0 mg/kg of nabilone (see below). Chlordiazepoxide in doses of 30 and 100 mg/kg caused a modest but consistent increase in both BP and HR (table 7; fig. 1).

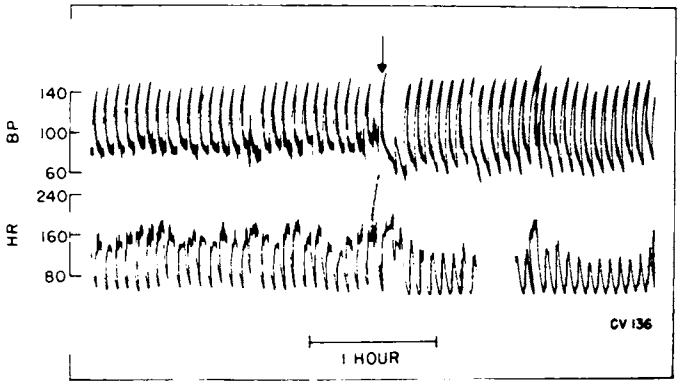

Fig. 2. Effects of canbisol on the cardiovascular response to 0.025 mg of norepinephrine (total dose each injection) intravenously. The norepinephrine was injected every 5.5 min and caused reasonably consistent increases in arterial blood pressure and decreases in heart rate. Canbisol (0.007 mg/kg) was injected through the same cannula as the norepinephrine and so there was a temporary interference with the repeated injections of norepinephrine until the cannula refilled with norepinephrine solution. When consistent responses were re-established, just before an injection, the blood pressure and heart rate were substantially lower than before the canbisol, but peak blood pressure after the norepinephrine injection was the same.

Nabilone caused a modest but prolonged (more than 3 hr) fall in BP in doses as low as 0.01 mg/kg i.v. and as high as 0.30 mg/kg i.v. (table 7; fig. 1), with little change in HR. A dose of 1.0 mg/kg i.v. caused an extraordinary effect, illustrated in figure 1. The BP fell, as with lower doses, but the period of hypotension was punctuated by irregular periods of hypertension lasting from a few minutes to as long as ½ hr. In going from the hypotensive to the hypertensive phase, the BP changed as much as 100 mm Hg, going from 50 to 150 mm Hg in a few minutes, as shown in figure 1. Meanwhile the monkey sat quietly in the chair, unresponsive to ordinary visual and auditory stimuli, with apparently hypertonic musculature. There was no evident change during the hypertensive episodes.

Nabilone i.m. caused insignificant effects until the huge dose of 3.0 mg/kg was given when there was a rise in BP, accompanied by a rise in HR (table 7).

Canbisol caused a modest decline in BP, with little change in HR at a dose as low as 0.003 mg/kg i.v., the lowest dose studied (table 7). Already at a dose as low as 0.01 mg/kg i.v. the fall in BP was sometimes profound and accompanied by a fall in HR (fig. 1). Increasing the dose did not cause more profound hypotension. The highest doses i.v., however, produced paroxysmal increases in BP superimposed on the prevailing hypotension as described for nabilone. The effect of canbisol i.m. was not appreciable at 0.03 mg/kg but profound at 10 mg/kg.

The effects of injected norepinephrine during the hypotension produced by canbisol have been studied. When 0.03 mg/kg i.v. of canbisol was given to a monkey receiving regular injections of norepinephrine i.v., the BP just before the injections fell some 20 mm Hg, but the peak level after the injection was unchanged (fig. 2). There was thus no antagonism of the CV effects of norepinephrine. The minimum HR, when the BP was highest and presumably the baroreceptor reflexes at their most active, was not changed by canbisol, but the maximum HR, just before the injection, was reduced by 40 beats/min (fig. 2).

When monkeys repeatedly pulled a t-bar, there was little effect on control BP but a modest increase in HR (fig. 3). Following a dose of canbisol that reduced BP from 100 mm Hg to less than 60 mm Hg, repeatedly pulling the bar caused a

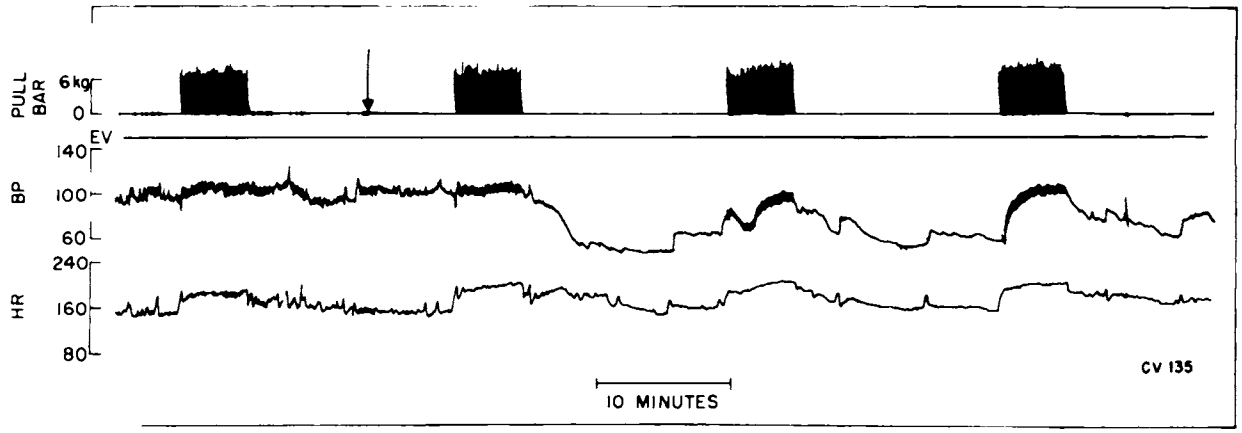

Fig. 3. Effects of canbisol on cardiovascular responses to hard physical work. The upper channel shows when the monkey was exerting a force of 6 kg every 3 to 4 sec. The EV channel would have shown when a shock was delivered (none was during the period shown). Before the injection of canbisol (0.03 mg/kg), at the time shown by the arrow, the work periods had little effect on blood pressure and caused a modest rise in heart rate. Blood pressure fell substantially about 15 min after the drug and subsequent work periods led to substantial rises in both blood pressure and heart rate. Even after the large dose of 0.03 mg/kg, causing profound cardiovascular effects, the monkey was still capable of hard physical labor.

large increase in BP, back to normal levels, while the HR changes were similar to control (fig. 3)

Discussion

Perhaps the most characteristic effects of cannabinoids on CV function are a tendency for BP to fall accompanied by a fall in HR. The characteristic effect is by no means always seen. Some of the reasons for the apparent variability have emerged from the present experiments and will be discussed under the following headings: predrug state of subject; non-monotonic dose-effect curve; and concomitant activities of subject.

Variability of CV effects of cannabinoids. *Predrug state.* Although Δ^9-THC lowered BP and HR in the rabbit with doses as low as 0.05 mg/kg i.v. and the BP in the rhesus monkey at 0.10 mg/kg i.v., it failed to have a recognizable effect in dogs at 0.25 mg/kg i.v. While it is possible that this last dose may have had a delayed effect, it is clear that we have not confirmed the finding of Friedman *et al.* (1977) that 0.10 or 0.25 mg/kg i.v. produces a profound fall in HR. There was a difference in vehicle in the two studies, Friedman *et al.* injecting the drug in a small volume of alcohol while we diluted the alcohol solution with several volumes of 0.05% Tween 80, but this difference appears inadequate to account for the difference in findings. A more likely explanation for the discrepancy relates to the starting condition of the dogs. The dogs of Friedman *et al.* started with average BP of about 140 mm Hg and HR or about 150 beats/min while our dogs averaged less than 100 mm Hg and 70 beats/min. If the CV effects of Δ^9-THC were largely related to a reduction in behavioral activities involving skeletal muscles, then the already low basal level of our dogs would provide little opportunity for further reduction by this mechanism.

The unanesthetized dog did not show the depressor and HR slowing effects of chlordiazepoxide found in anesthetized dogs and cats. Ordinary doses of chlordiazepoxide were similarly without CV effects in the rabbit and rhesus monkeys. Massive doses (30 and 100 mg/kg i.v.) in the rhesus monkey caused a sustained increase in both BP and HR. This effect has probably little relevance to clinical usage except to suggest that even with enormous overdosage there is little danger of CV collapse, such as occurs, for example, with overdosage of barbiturates.

Non-monotonic dose-effect curve. While Δ^9-THC caused a fall in BP and HR in the rabbit in doses as low as 0.05 mg/kg, the effect did not increase with increasing dose and was less at 0.20 mg/kg. In monkeys, likewise, Δ^9-THC caused a fall in BP at 0.1 mg/kg but not at 0.3 mg/kg, and at 3 mg/kg there were both hypotensive and hypertensive periods.

Nabilone in the rabbit caused a fall in BP and HR at 0.064 mg/kg but not in HR at 0.125 mg/kg. In the monkey, nabilone caused a fall in BP at doses from 0.1 to 0.3 mg/kg, but 1.0 mg/kg caused periods of both hypotension and hypertension.

Canbisol caused a fall in BP and HR at 0.001 mg/kg but no fall in BP and an increase in HR at 0.016 mg/kg in the rabbit. In the dog, canbisol produced slight hypotension at 0.004 mg/kg, an effect that was not intensified with higher doses. Finally, canbisol i.v. caused a modest decline in BP at 0.003 mg/kg in the monkey but at 0.1 mg/kg caused periods of both hypotension and hypertension.

It is apparent that the effects of all these cannabinoids on CV functions is non-monotonic, the effects not always increasing and sometimes reversing at higher doses. It is obvious that such a phenomenon contributes to the difficulties in studying the effects and has no doubt contributed to the the unsatisfactory state of knowledge on the CV effects of cannabinoids. The obvious inference is that the cannabinoids have two separate effects: first, a tendency to lower BP and HR and then, second, as doses are increased a tendency to increase both. With very large doses the first and second effects may alternate in preponderance, so that hypotensive and hypertensive periods succeed one another (Fig. 2).

Concomitant activities of subject. The hypotensive effects of canbisol could be overcome by vigorous exercise. Such a finding further complicates the interpretation of reported CV effects of cannabinoids, and limits the value of studies on anesthetized subjects.

Possible mechanisms. That the hypotensive effects of cannabinoids are physiologically surmountable suggests a mechanism for both the non-monotonic dose-effect curve and the paroxysmal hypertension with high doses. The most obvious explanation of the increase in blood pressure with exercise is that it is the result of increased venous return with consequent increased cardiac output, that is, as a direct effect of the skeletal muscle contractions. The hypotensive effect of modest doses conversely could be the consequence of generalized skeletal muscle hypotonicity. Higher doses could produce paroxysmal or sustained strong tonic activities of a major proportion of the skeletal muscle mass as part of the behavioral effects, thus overcoming the hypotensive effects. All of the effects could occur despite a functionally intact autonomic nervous system, and, indeed, it is known that cannabinoids do not antagonize norepinephrine (here confirmed), block ganglia, relax vascular smooth muscle or interfere with contractility of the myocardium. That skeletal muscle activities may be crucial in the CV effects of cannabinoids is compatible with the consensus of workers on the CV effects of cannabinoids that the effects are mediated by effects on the central nervous system (see, for example, Cavero *et al.*, 1973) as skeletal muscle activity is very directly controlled by the central nervous system. The possibilities of a direct effect of cannabinoids on central CV regulating mechanism cannot be excluded, and the different cannabinoids might differ greatly in potency in this regard. The sustained effects of small daily doses may have therapeutic potential, but the effects are hard to study experimentally as the effects of small doses are small, and attempts to intensify them by increasing dosage result in a whole new and interfering set of effects.

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