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CANNABIS, CATECHOLAMINES, RAPID EYE MOVEMENT SLEEP AND AGGRESSIVE BEHAVIOUR

E.A. CARLINI, C.J. LINDSEY & S. TUFIK

Departmento de Psicobiologia, Escola Paulista de Medicina, Rua Botucatu, 862–1° andar, 04023 São Paulo, Brasil

1 Previous work from our laboratory has shown that cannabis induces aggressive behaviour in rats that have been deprived of rapid eye movement (REM) sleep. It was suggested that this effect was related to brain catecholamines, with dopamine playing an agonist role and noradrenaline an inhibitory one. The present paper describes new experiments dealing with this subject.

2 Previous REM sleep-deprivation enhanced both Δ^9-tetrahydrocannabinol (THC)-induced hypothermia and nomifensine effects on aggressive behaviour.

3 A marihuana extract decreased brain dopamine turnover in REM sleep-deprived rats, an effect not observed in non-deprived rats. Noradrenaline metabolism was not altered.

4 Fighting behaviour was elicited in REM sleep-deprived rats treated with 4 different dopamine-β-hydroxylase inhibitors.

5 Apomorphine, nomifensine and Δ^9-THC administered to non-deprived rats pretreated with bis(4-methyl-1-homopiperanzinyl-thiocarbonyl) disulphide (Fla-63), induced fighting behaviour.

6 Nomifensine and apomorphine induced fighting in non-deprived rats pretreated with Δ^9-THC.

7 Clonidine inhibited the fighting elicited in REM sleep-deprived rats by either Δ^9-THC or Fla-63 pretreatment.

8 The data are discussed in terms of the influence of REM sleep-deprivation (or the stress associated with deprivation) on the response to dopaminergic drugs and cannabis. Taken together they emphasize the participation of brain dopamine and noradrenaline systems in the aggressive behaviour studied.

Introduction

In previous papers we have tried to relate the aggressive behaviour induced by cannabis (the word cannabis, as used in the text, can mean marihuana extract or its active principles Δ^9- or Δ^8-tetrahydrocannabinol (THC)) in rapid eye movement (REM) sleep-deprived rats to brain catecholamine systems by means of pharmacological manipulations. It was suggested that an imbalance of the dopaminergic and noradrenergic systems could be facilitating the cannabis effect. Briefly, neuroleptics and α-methyl-*p*-tyrosine decrease or inhibit cannabis-induced aggressiveness in REM sleep-deprived rats, whereas L-DOPA administration increases fighting (Carlini & Lindsey, 1974). Conversely, noradrenaline depletion with Fla-63, a noradrenaline synthesis inhibitor (Corrodi, Fuxe, Hamberger & Ljungdahl, 1970), increases cannabis-induced aggressive behaviour (Carlini & Lindsey, 1974) whereas intraventricularly administered noradrenaline decreases fighting (Musty, Lindsey & Carlini, 1976). Thus, it appears that dopamine plays an agonist role in the development of this behaviour while high levels of noradrenaline inhibit the aggressiveness.

Concurrently we have been interested in another aspect of the problem: the effects of REM sleep-deprivation on the responsiveness of the dopaminergic system, since we believe that REM sleep-deprivation sensitizes the brain to some cannabis effects (i.e. aggressive behaviour), which may be mediated through dopamine. Experiments showed that REM sleep-deprivation enhanced the effects of apomorphine in different behavioural tests, including aggressive behaviour, suggesting that dopamine receptor supersensitivity may be occurring after REM sleep-deprivation (Carlini, Lindsey & Tufik, 1976; Tufik, Lindsey & Carlini, 1977). This hypothesis offers an explanation for some of our previous findings, as for example, the large amount of aggressive behaviour obtained with apomorphine after REM sleep-deprivation with doses that did not elicit fighting in

normal rats (Carlini & Lindsey, 1974). Another example was the finding that Fla-63 induces aggressive behaviour in REM sleep-deprived rats and not in non-deprived animals (Carlini & Lindsey, 1974). In this situation, decrease of noradrenaline levels by Fla-63 would facilitate aggressive behaviour, while REM sleep-deprivation rendering the dopaminergic system hyper-responsive would, thus, induce fighting behaviour.

In this paper we describe some experiments bearing on different aspects of the discussion above. Experiments I, II and III test the effects of REM sleep-deprivation on the response to nomifensine (I), a drug that acts on the dopaminergic system, and on the effects of cannabis (II and III); experiments IV, V, VI and VII are concerned with manipulations of the dopaminergic and noradrenergic systems and aggressive behaviour.

Methods

Naive male Wistar rats 80–120 day old weighing 240–300 g bred in our own colony were used for the experiments. Behavioural observations were carried out in wire cages measuring 20 x 20 x 30 cm or the animals were placed in small wooden boxes measuring 10 x 10 x 20 cm. REM sleep-deprivation chambers consisted of 23 x 23 x 40 cm pails containing 4 cm of water. An overturned flower pot (5 cm high) was placed in the water, its base being 1 cm above water level. The base of the flowerpot (platform) was either 6 or 14 cm in diameter.

Drugs

The following drugs were used: alcoholic extract of *Cannabis sativa* containing 83.4% of Δ^9-THC, 16.7% of cannabinol and no detectable cannabidiol, prepared as described by Carlini & Kramer (1965); Δ^9-tetrahydrocannabinol (NIDA); nomifensine kindly supplied by Hoescht; bis (4-methyl-1-homopiperanzinyl-thiocarbonyl) disulphide (Fla-63; Aldrich Chemical Company); sodium diethyldithiocarbamate (DDTC; Merck Darmstadt); clonidine (C.H. Boehringer); 1-phenyl-3-(2-thiazolyl) 2-thiourea (U-14624, Aldrich Chemical Company) kindly supplied by Dr W.M. Davis; apomorphine (Sandoz) and fusaric acid (Sigma Chemical Company); α-methyl-*p*-tyrosine-methyl ester (AMPT; Sigma Chemical Company). All drugs were suspended in Tween-80 in distilled water with the exception of apomorphine and clonidine which were dissolved in distilled water. Control solutions consisted of Tween-80 1–2% in water or only water according to the drug used. All drugs were injected by the intraperitoneal route, in a volume of 1.0 ml/kg.

Procedure

The animals used were subject to one of the different environmental conditions. The REM sleep-deprived groups and the stress control groups (controls) were placed in the deprivation chambers for 72 or 96 h before the beginning of the experiment. REM sleep-deprived rats were placed on 6 cm platforms while controls were placed on 14 cm platforms. Non-deprived rats were taken directly from their home cages. The time elapsed between the removal from the deprivation chambers and the beginning of the experiment was approximately 5 minutes.

Aggressive behaviour

Aggressive behaviour was scored by placing pairs of identically treated rats of similar body weight in wire cages. The occurrence of aggressive behaviour was recorded in seconds for the following 2 or 3 hours. The observation period was divided into 30 or 15 min intervals. Aggressiveness, aggressive behaviour or fighting are used as synonyms to mean the time both animals remained in mutual upright posture or when one animal forced its partner to assume different patterns of submissive postures. No other aspects of behaviour elicited are discussed in this paper.

Body temperature

Rats were placed individually in small wooden boxes. Temperature was taken before drug treatment and then 15, 30, 60, 120 and 240 min afterwards, by introducing a clinical thermometer 4 cm into the rectum. The reading was made 1 min after the mercury column had stabilized.

Biochemical assays

Animals were decapitated, brains rapidly removed, washed in cool 0.9% w/v NaCl solution (saline) and homogenized in 0.4 N $HClO_4$. The homogenates were stored in a freezer for 24 to 48 h before assay. Dopamine and noradrenaline were measured according to Anton & Sayre (1962; 1964).

Results

Experiment I

Aggressive behaviour has been described for apomorphine (Carlini & Lindsey, 1974) and amphetamine (Ferguson & Dement, 1969) in REM sleep-deprived rats. Knowing that REM sleep-deprivation enhances several apomorphine effects (Carlini *et al.*, 1976; Tufik *et al.*, 1977) it would be interesting to know whether the same effect occurs with another drug, nomifensine, reported to be a

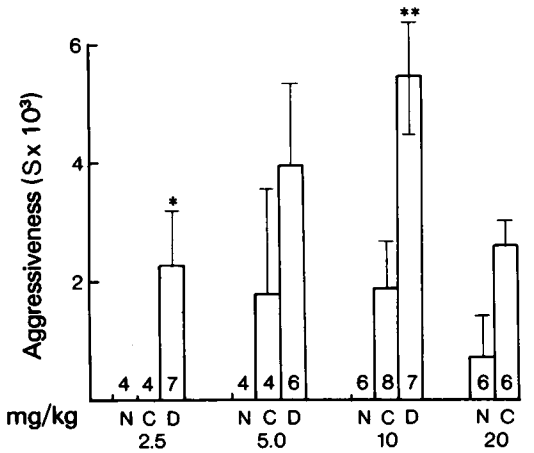

Figure 1 Mean duration of fighting behaviour measured in seconds for non-deprived (N), REM sleep-deprived (D) and stress control (C) rats, after nomifensine administration. Vertical lines over columns represent the standard error; the figures in columns indicate the numbers of pairs tested. Asterisks denote difference from stress control and from non-deprived animals (*$P \leqslant 0.05$; **$P \leqslant 0.01$; Student's t test, following one way analysis of variance).

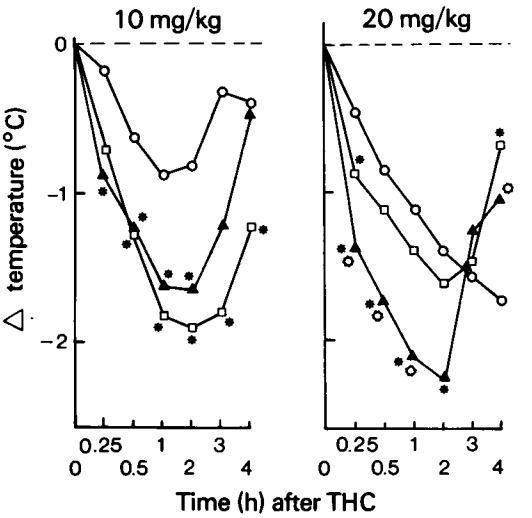

Figure 2 Mean drop in body temperature for non-deprived (○), REM sleep-deprived (▲) and stress control (□) rats, after 10 and 20 mg/kg of Δ^9-tetrahydrocannabinol. Solid stars indicate significant difference from non-deprived rats while open stars denote statistical difference from stress controls (P at least 0.05; one tailed Student's t test, following one way

potent inhibitor of dopamine uptake (Hunt & Kannengiesser, 1974).

Three groups of rats, non-deprived, stress controls and 72 h REM sleep-deprived were injected with 2.5, 5.0 and 10 mg/kg of nomifensine; 20 mg/kg was administered only to the first 2 groups. The animals were paired and aggressive behaviour scored for the next 2 hours.

The results in Figure 1 show that the REM sleep-deprived animals (2.5 and 10 mg/kg) fought more and at lower doses than did controls and non-deprived animals. Stress control animals also fought more than non-deprived rats, reaching significance at 10 mg/kg dose ($P \leqslant 0.05$).

Experiment II

The preceding experiment indicated the hyper-responsiveness to a drug acting on the dopaminergic system after animals had been submitted to REM sleep-deprivation. In this and the next experiment we investigated the influence of deprivation on the effects of Δ^9-THC or cannabis. Body temperature, possibly controlled by the dopaminergic system in the ventral hypothalamus (Reid, 1975) and known to be lowered by Δ^9-THC, was compared in non-deprived, stress controls and 72 h REM sleep-deprived rats.

The results in Figure 2 show that Δ^9-THC 10 and 20 mg/kg induced a drop in body temperature in REM sleep-deprived rats that was always larger than that obtained in the non-deprived group; for the 20 mg/kg dose the effect in REM sleep-deprived animals was larger than in the stress control group. Δ^9-THC 10 mg/kg also induced a large drop in body temperature in the stress control group which was significantly greater than in the non-deprived animals.

Experiment III

No consistent alterations of brain catecholamine metabolism have been reported after acute cannabis injections given to rats under normal conditions. In view of the results obtained in the first two experiments, an eventual effect of cannabis on catecholamine turnover, due to previous REM sleep-deprivation, became a possibility.

Two separate experiments were carried out in order to assess dopamine turnover in REM sleep-deprived and non-deprived rats treated with cannabis extract. In experiment (a) turnover was measured according to Brodie, Costa, Dlabac, Neff & Smookler (1966). One-hundred and twenty non-deprived or 4 day REM sleep-deprived rats were injected with marihuana extract 10 mg/kg or control solution and 30 min later injected with 250 mg/kg of AMPT. The animals were killed 0, 1, 2, 4 and 8 h later for dopamine and noradrenaline assay. The REM sleep-deprived rats were either paired (allowed to fight) in wire cages or kept isolated in small

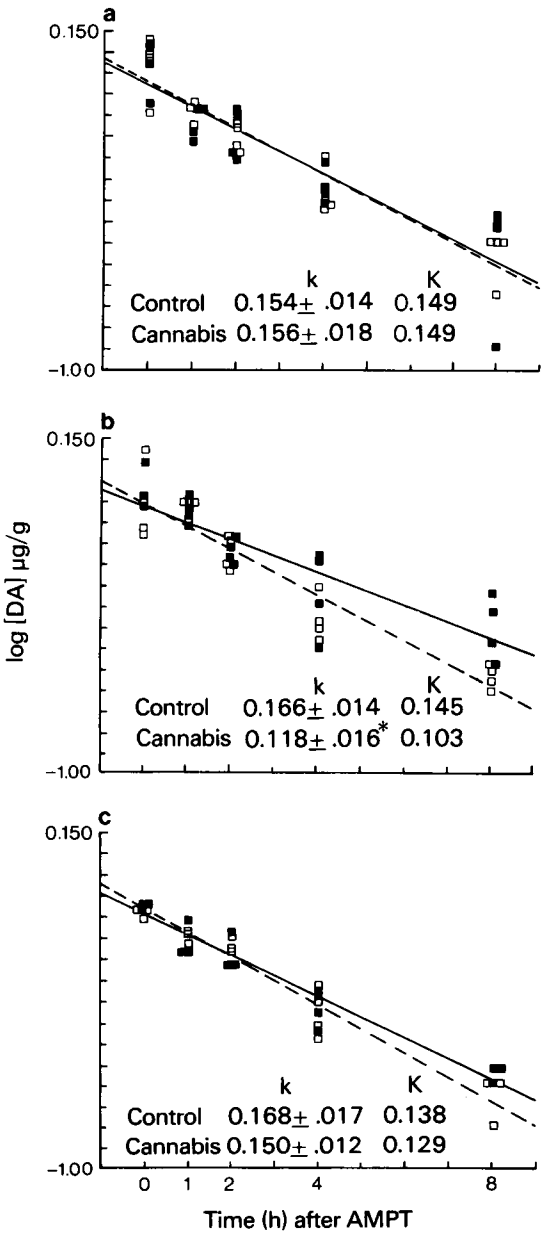

Figure 3 Disappearance rate of dopamine (DA) in whole brain, after α-methyl-*p*-tyrosine (AMPT), of rats treated with control solution (□---□) or cannabis extract (■——■) 10 mg/kg. Rate constant of dopamine efflux [k(h^{-1})] and turnover rate (K=µg kg^{-1} h^{-1}). (a) Non-deprived animals; (b) REM sleep-deprived rats kept individually after cannabis or control solution administration; (c) REM sleep-deprived rats paired after injections and allowed to fight. (*Differs from control-injected animals, $P \leqslant 0.05$, least squares method). Curves for disappearance rates of noradrenaline are not shown as no differences were found.

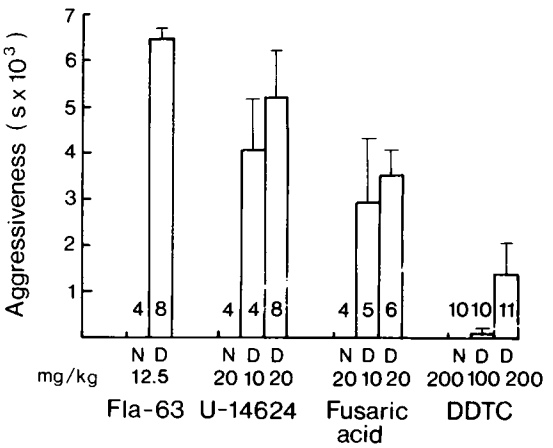

Figure 4 Fighting induced by dopamine-β-hydroxylase inhibitors (Fla-63, U-14624, fusaric acid or DDTC) in REM sleep-deprived (D) and non-deprived (N) rats. For details see Figure 1.

wooden boxes in order to exclude any eventual effect of fighting on catecholamine turnover; non-deprived rats were kept isolated. The experiment was repeated (b) with the only difference being that amine turnover was estimated as recommended by Lidbrink, Corrodi, Fuxe & Olson (1972). The animals (46) were injected with marihuana 10 mg/kg or control solution; 30 min later they were injected with AMPT 400 mg/kg and were killed 0 or 4 h later for assays.

Cannabis (Figure 3 and Table 1) reliably decreased dopamine turnover rate in REM sleep-deprived rats that were isolated, but had no effect on non-deprived animals. On the other hand, the effects of cannabis were not evident in the REM sleep-deprived animals when they were allowed to fight. Noradrenaline turnover was not altered under any of the experimental conditions.

Experiment IV

Fla-63, a noradrenaline synthesis inhibitor, when administered to REM sleep-deprived rats induces prolonged fighting between paired animals (Carlini & Lindsey, 1974). This effect we believe is due to noradrenaline depletion in the deprived animals. Thus, it would be interesting to know whether other noradrenaline synthesis inhibitors, with different chemical structures, elicit aggressive behaviour. The effects of DDTC (Carlsson, Lindqvist, Fuxe & Hökfelt, 1966) 100 and 200 mg/kg administered 5 h before the end of the 96 h deprivation period, U-14624 (Johnson, Boukma & Kim, 1970) 10 and 20 mg/kg and fusaric acid (Nagatsu, Hidaka, Kusuya, Takeya, Umezawa, Takeuchi & Suda, 1970) 10 and 20 mg/kg,

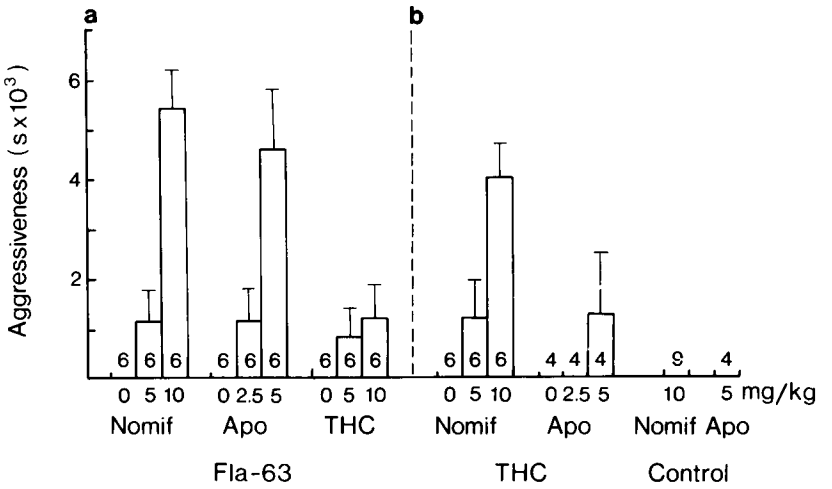

Figure 5 (a) Fighting induced by apomorphine (Apo) nomifensine (Nomif) and Δ^9-tetrahydrocannabinol (THC) in non-deprived rats pretreated with Fla-63; (b) fighting induced by Δ^9-THC plus apomorphine or nomifensine in non-deprived animals. For other details see Figure 1.

were compared with 12.5 mg/kg Fla-63; the latter drugs were administered 4 h before the end of 96 h of deprivation. After deprivation, animals were paired and aggressive behaviour scored for 2 hours.

All four drugs (Figure 4) induced fighting in REM sleep-deprived rats, DDTC doing so only at the 200 mg/kg dose. None of the drugs tested induced fighting in the non-deprived groups.

Experiment V

As suggested in the introduction, the aggressive behaviour induced in REM sleep-deprived rats by Fla-63 could be due to both a decrease of the inhibitory influences of noradrenaline and to an increase in the dopaminergic function after deprivation. If this theory is correct then it should be possible to elicit aggressive

Table 1 Influence of cannabis extract (10 mg/kg) on the depletion of brain catecholamines after inhibition of tyrosine hydroxylase with α-methyl-*p*-tyrosine (AMPT 400 mg/kg) in REM sleep-deprived and non-deprived rats

Rat condition			*Brain level (μg/g ± s.d.) at 0 and 4 h after administration of AMPT*			
			Dopamine		*Noradrenaline*	
REM depriv.	*Housing*	*Drug*	*0 h*	*4 h*	*0 h*	*4 h*
None	Indiv.	Control soln.	0.91 ± 0.06	0.51 ± 0.11	0.46 ± 0.05	0.28 ± 0.05
4 days	Indiv.	Control soln.	1.00 ± 0.13	0.59 ± 0.03	0.49 ± 0.05	0.34 ± 0.04
None	Indiv.	Cannabis	0.91 ± 0.09	0.50 ± 0.05	0.41 ± 0.07	0.27 ± 0.02
4 days	Indiv.	Cannabis	1.01 ± 0.23	0.67 ± 0.09*†	0.48 ± 0.09	0.34 ± 0.07
4 days	Paired	Control soln.	0.94 ± 0.10	0.48 ± 0.06	0.42 ± 0.03	0.26 ± 0.03
4 days	Paired	Cannabis	0.89 ± 0.14	0.55 ± 0.09	0.46 ± 0.11	0.29 ± 0.04

* Differs significantly from REM sleep-deprived control solution-injected animals ($P \leqslant 0.01$; one tailed Student's *t* test).
† Differs significantly from non-deprived cannabis-injected animals ($P \leqslant 0.0005$; one tailed Student's *t* test).

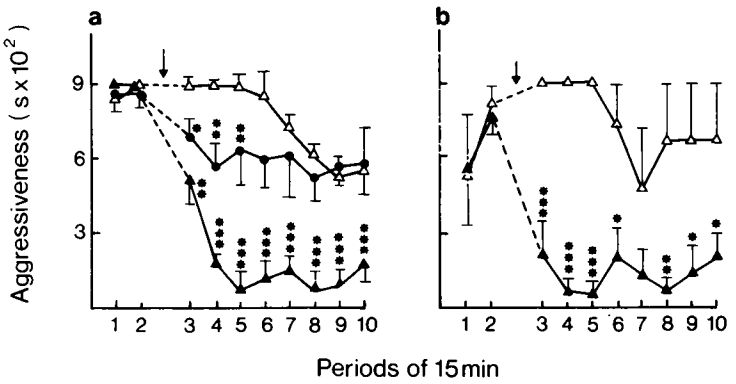

Figure 6 Effects of control solution (△), clonidine 50 μg/kg (●) or 100 μg/kg (▲) on fighting behaviour induced by marihuana extract (a) or Fla-63 (b) in REM sleep-deprived rats. The arrows indicate clonidine or control solution injections. Asterisks indicate significant differences from control solution (*$P \leqslant 0.05$; **$P \leqslant 0.02$; ***$P \leqslant 0.01$; Student's t test, following one way analyses of variance).

behaviour by stimulating pharmacologically the dopaminergic system in rats pretreated with a dopamine-β-hydroxylase inhibitor.

Non-deprived rats were treated with 12.5 mg/kg of Fla-63 and 4 h later were injected with either apomorphine 2.5 and 5.0 mg/kg, or nomifensine 5.0 and 10 mg/kg, or Δ^9-THC 5.0 and 10 mg/kg. The latter drug was included for comparative purposes. After injection the animals were paired and aggressive behaviour scored.

All drugs tested induced fighting (Figure 5a) in non-deprived rats pretreated with Fla-63; apomorphine 5 mg/kg and nomifensine 10 mg/kg induced the greatest amount of fighting.

Experiment VI

The combination of cannabis with apomorphine and nomifensine was also tested. According to Musty *et al.* (1976) an imbalance between the dopaminergic and noradrenergic systems associated with cannabis could lead to aggressive behaviour. Noradrenaline depletion together with cannabis, in fact, produced such an effect. It remained to be seen whether dopaminergic stimulation in Δ^9-THC-treated animals would induce fighting.

Non-deprived rats were treated with Δ^9-THC 5 mg/kg or control solution and 30 min later were injected with either nomifensine (0, 5.0 and 10 mg/kg) or apomorphine (0, 2.5 and 5.0 mg/kg); they were paired and observed for 2 hours. Nomifensine (Figure 5b, 10 mg/kg) plus Δ^9-THC produced a substantial amount of fighting. Of the four pairs treated with apomorphine 5.0 mg/kg, only one pair fought; however, the fighting was very intense. No fighting was observed when nomifensine or apomorphine were administered to rats previously treated with control solution.

Experiment VII

Phenoxybenzamine (Carlini & Lindsey, 1974) and dopamine-β-hydroxylase inhibitors (Experiment IV) have been shown to induce aggressive behaviour in REM sleep-deprived rats, suggesting that noradrenaline may play an inhibitory role in aggressive behaviour. Also noradrenaline injected intraventricularly decreases cannabis-induced fighting. To characterize further the role played by noradrenaline, the following experiment was done: aggressive behaviour was elicited in REM sleep-deprived rats either by injection of cannabis extract 10 mg/kg at the end of deprivation, or by injection of Fla-63 12.5 mg/kg, 4 h before the end of deprivation time. The animals were paired and allowed to fight for two 15 min periods, after which the rats treated with cannabis were injected with 0, 50 or 100 μg/kg of clonidine, an adrenoceptor agonist (Haeusler, 1974; Svensson, Bunney & Aghajanian, 1975), 6 pairs per dose. The rats treated with Fla-63 were injected either with 0 or 100 μg/kg of clonidine, 4 pairs per dose. Aggressive behaviour was scored for the eight following 15 min intervals.

Clonidine 100 μg/kg reduced fighting in the deprived rats treated with Fla-63 as well as with marihuana for the entire observation period (Figure 6a, b). Clonidine 50 μg/kg administered to deprived rats treated with cannabis extract had a shorter effect, reducing the fighting only up to 45 min after injection (Figure 6a).

Discussion

Previous REM sleep-deprivation alters cannabis effects from depression to a state of irritability and aggression in rats. REM sleep-deprived rats treated

with cannabis fight for long periods of time compared with non-deprived animals treated with the same drug (Alves, Goyos & Garlini, 1973).

The observed influence of REM sleep-deprivation on cannabis effects was extended to two other situations. In experiment II, REM sleep-deprivation was shown to increase Δ^9-THC hypothermia and in experiment III marihuana extract decreased dopamine turnover in whole brain in REM sleep-deprived rats but had no detectable effects on dopamine metabolism in non-deprived animals. When REM sleep-deprived rats treated with marihuana were paired and allowed to fight (Figure 3, Table 1) the difference in dopamine turnover as compared with control solution-injected animals, was no longer significant, suggesting that fighting may increase dopamine turnover. A similar effect of fighting on catecholamine turnover was observed in rats for noradrenaline (Stolk, Conner, Levine & Barchas, 1974) and in mice for dopamine and noradrenaline (Modigh, 1973, 1974). Experiments I and II also provide indirect evidence that cannabis may be acting through dopaminergic mechanisms. Body temperature is altered by apomorphine administration (Fuxe & Sjöqvist, 1972) and decrease in dopamine turnover can be induced by direct dopamine receptor agonists (Goldstein, Freedman & Backstrom, 1970).

More evidence supporting the involvement of dopaminergic mechanisms in cannabis action comes from other comparisons. Not only does REM sleep-deprivation change cannabis or Δ^9-THC effects but it also induces an increased response to apomorphine (Carlini *et al.*, 1976; Tufik *et al.*, 1977) and to nomifensine (experiment I). Similarly, cannabis induces aggressive behaviour in 6-hydroxydopamine (6-OHDA) pretreated rats (Musty *et al.*, 1976) and in morphine-abstinent rats (Carlini & Gonzalez, 1972). Opiate (Gianutsos, Hynes, Puri, Drawbaugh & Lal, 1974) and 6-OHDA (Barnes, Cann, Karczmar, Kindel & Longo, 1973) administration are thought to induce dopamine receptor supersensitivity. Other data in the literature can be found that are indicative of possible dopaminergic actions of cannabis. Δ^9-THC-induced inhibition of prolactin secretion (Kramer & Ben David, 1974) and induction of turning behaviour (Waters & Glick, 1973; Hine, Friedman, Torrelio & Gershon, 1975) serve as examples.

A question that may be asked is, if the changes that were observed in response to nomifensine and Δ^9-THC or marihuana are due to REM sleep-deprivation *per se* or to the stress derived from the deprivation procedure. In experiments I and II both stress control groups differed from non-deprived animals showing an increased response to nomifensine or Δ^9-THC. Littleton & MacLean (1974) reported a decrease in dopamine depletion after AMPT in rats treated with Δ^8-THC submitted to stressful situations as food deprivation or cold exposure. Thus, it seems that stress, if not the only variable contributing to these alterations, is nevertheless an important factor. The most important aspect of these data, however, is that both of the manipulations referred to above, food deprivation and cold exposure, alter the behavioural effects of cannabis in a similar way to REM sleep-deprivation. Cannabis injected in either starved or cold-exposed rats elicits fighting in these animals (Carlini, Hamoaui & Märtz, 1972).

Five different manipulations which alter the effects of cannabinoids from depression to agressiveness have been referred to. Three of them, REM sleep-deprivation, abstinence from morphine and 6-OHDA pretreatment have been related to an increase in dopaminergic response to direct agonists. The others, food deprivation and cold exposure, together with REM sleep-deprivation, decrease dopamine turnover when associated with Δ^8-THC or cannabis injections.

Confirming results with Fla-63, three other noradrenaline synthesis inhibitors induced aggressive behaviour in REM sleep-deprived rats (Experiment IV). Clonidine, and adrenoceptor agonist (Experiment VII), decreased fighting in deprived animals treated with Fla-63, or marihuana. These results strengthen the hypothesis that noradrenaline, unlike dopamine, plays an inhibitory role in the development of some forms of aggressive behaviour (Geyer & Segal, 1974; Musty *et al.*, 1976). In fact, substantial fighting was elicited by nomifensine and apomorphine in rats which had undergone noradrenaline depletion (Experiment V).

Aggressive behaviour has been elicited by DDTC and pargyline (Scheel-Krüger & Randrup, 1968), a combination of drugs which could have a similar effect on brain catecholamines as Fla-63 plus nomifensine or apomorphine; however, our data contrast with those of Senault (1974) who found that Fla-63 (and DDTC) decreased apomorphine-induced fighting. The doses of Fla-63 employed were 2 and 4 times larger than used in this paper; the latter dose killed all animals (Senault, 1974). Also differences in route and dose of apomorphine administration (the doses used here do not induce fighting in non-manipulated animals) could account for the discrepancy.

Our primary aim was to gather information on how alterations of neurohumoral systems influence cannabis effects and thus gain insight into possible mechanisms of cannabis action. Aggressive behaviour can be elicited by catecholamine manipulation as well as by cannabis under certain circumstances. The environmental manipulations which lead to aggressive behaviour are held to alter the dopaminergic response to direct agonists or to alter cannabis effects on dopamine metabolism. Pharmacological manipulations which change the effects of cannabis to aggressiveness alter the dopamine/noradrenaline balance. Although evidence for an action on the dopaminergic system of cannabis has been presented, many of its effects (Masur & Khazam, 1970; Drew & Miller, 1974; Graham, Lewis & Li, 1974) cannot be

explained solely by an interaction with dopamine. It seems likely that cannabis acts on different mechanisms which in turn interact with the transmitter systems discussed.

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