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Effects of Delta-9-Tetrahydrocannabinol Exposure on Adrenal Medullary Function: Evidence of an Acute Effect and Development of Tolerance in Chronic Treatments

F. RODRÍGUEZ DE FONSECA, J. J. FERNÁNDEZ-RUIZ, L. MURPHY,*
J. C. ELDRIDGE,† R. W. STEGER* AND A. BARTKE*

Department of Biochemistry, Faculty of Medicine, Complutense University, 28040, Madrid, Spain
**Department of Physiology, School of Medicine, Southern Illinois University, Carbondale, IL 62901-6503*
†Department of Physiology and Pharmacology, Bowman Gray School of Medicine
Wake Forest University, Winston-Salem, NC 27103

RODRÍGUEZ DE FONSECA, F., J. J. FERNÁNDEZ-RUIZ, L. MURPHY, J. C. ELDRIDGE, R. W. STEGER AND A. BARTKE. *Effects of delta-9-tetrahydrocannabinol exposure on adrenal medullary function: Evidence of an acute effect and development of tolerance in chronic treatments.* PHARMACOL BIOCHEM BEHAV **40**(3) 593–598, 1991.—Previous studies have shown that the secretion of several stress-related hormones can be altered by exposure to marihuana or its purified constituents. The purpose of this study was to examine changes in adrenal medullary function caused by acute, subchronic and chronic treatments with two different doses of delta-9-tetrahydrocannabinol (THC). Acute exposure to THC caused a significant decrease in the adrenal medulla contents of both norepinephrine (NE) and epinephrine (E) and a significant increase in the E/NE ratio. These effects were mainly observed with the highest dose of THC, but they were not accompanied by a statistically significant decrease in adrenal medulla tyrosine hydroxylase activity, the rate-limiting enzyme in the catecholamine (CA) synthesis. These effects disappeared after seven or fourteen days of a daily THC treatment, which suggests the development of tolerance to this drug. Analysis of plasma PRL, ACTH and corticosterone levels showed some THC-related changes in these hormones. THC-induced modifications in ACTH and corticosterone were not in parallel to the changes in the adrenal medulla function, whereas those effects of acute THC on PRL release were statistically correlated with decreases of CA contents following acute THC. In conclusion, acute exposure to THC caused an alteration in the adrenal medullary function, reflected by a fall in endogenous stores of both CAs which could influence the adrenal medullary response to stress situations. This acute effect of THC could be mediated by the pituitary secretion of PRL, although the possibility of an effect directly exerted on the adrenal medulla chromaffin cells should be also considered. This acute effect disappeared after prolonged treatments, suggesting the development of tolerance to this drug.

Cannabinoids Delta-9-tetrahydrocannabinol Adrenal medulla Catecholamine Tyrosine hydroxylase

THE secretion of several stress-related hormones can be affected by exposure to marihuana or its purified constituents. Thus, acute or chronic exposures to delta-9-tetrahydrocannabinol (THC), the main psychoactive ingredient of marihuana, has been shown to cause a pituitary-adrenal activation (7), with increases in plasma ACTH and corticosterone levels and adrenal weights in rats (18, 21, 24), and a decrease in plasma prolactin (PRL) levels in rats (16, 20, 30), mice (4) and monkeys (1). Moreover, THC has been shown to be able to alter the neurotransmitter activity in brain areas related to the control of the stress response (6,28).

Less information is available on the effects of cannabinoids on adrenal medullary function (28), which has been greatly involved in the stress response (19). In the present work, we examined the effects of acute and chronic treatments with THC on catecholamine (CA) contents and tyrosine hydroxylase (TH) activity, the rate-limiting enzyme in CA synthesis, in the adrenal medulla of adult male rats. The study was carried out with two doses of THC: a low dose (0.5 mg/kg body weight) and a high dose (5 mg/kg body weight), both given orally. These doses were chosen because they produce blood THC levels in the range of those reported to produce psychological and physiological effects in various animal models (1). In order to validate the efficiency of the treatment, we monitored the plasma levels of THC in each animal at the time of sacrifice. Moreover, we studied the possible involvement of several pituitary and adrenal hormones (PRL, ACTH and corticosterone) in mediating the effects of cannabinoids on the adrenal medulla. These hormones have been shown to be involved in the regulation of adrenal medullary function (3, 11, 13, 33) and their release can be affected by cannabinoids (2, 4, 7, 16, 18, 20, 21, 24, 30).

METHOD

Animals

Male HSD: Sprague-Dawley (SD) BR rats were used in these studies. They were purchased from Harlan Sprague-Dawley (Indianapolis, IN) and housed in a room with controlled photoperiod (0800–2000 h light on) and temperature (23 ± 1°C). They had constant access to food and water. At adult age (>2 months old), they were fed (0900 h) either a low dose (0.5 mg/kg weight) or a high dose of THC (5 mg/kg weight). THC was obtained from the National Institute of Drug Abuse and prepared in sesame oil for feeding. Control animals were fed vehicle alone (0.1 ml). In the first experiment, animals were sacrificed one hour after feeding in order to examine the acute effects of THC (ACUTE experiment). In the second experiment, animals were fed THC daily and sacrificed after either seven (SUBCHRONIC experiment) or fourteen days of treatment (CHRONIC experiment). Sacrifice was accomplished by rapid decapitation in order to diminish the acute stress response of endocrine secretion. After decapitation, trunk blood was collected in tubes containing 6% EDTA, centrifuged for 10 minutes at 2500 × g at 4°C, and the plasma removed and stored frozen at −20°C for measurements of THC, PRL, ACTH and corticosterone. Adrenals were removed, immediately frozen, and kept at −70°C until assayed for CA contents and TH activity.

Catecholamine Analysis

Norepinephrine (NE) and epinephrine (E) concentrations in the adrenals were analyzed using HPLC with electrochemical detection according to the procedure described by Steger et al. (32). Adrenals were cleaned, the cortex was discarded and the medulla was weighed and homogenized in 100 volumes of ice-cold 0.2 N perchloric acid containing 0.5 mM sodium bisulfite and dihydroxybenzylamine as internal standard. Details of the method used have been previously published (10). Catecholamine concentrations were expressed as ng/mg of tissue weight.

Assay of Tyrosine Hydroxylase Activity

Tyrosine hydroxylase activity was evaluated according to the method described by Nagatsu et al. (26). Adrenals were weighed and homogenized in 30 volumes of 0.25 M sucrose. An aliquot of homogenate (corresponding to 1 mg of tissue) was assayed at 37°C in 0.1 ml of incubation media containing 0.1 M sodium acetate, 0.1 mg/ml catalase, 1 mM 6-methyl-5,6,7,8-tetrahydropterine (prepared in 1 M mercaptoethanol solution) and 0.2 mM L-tyrosine. For the blank incubation, D-tyrosine was used as substrate instead of L-tyrosine. Blank tubes with 1 μM L-dopa were also used as internal standards for each tissue. After 10 minutes of incubation, the reaction was stopped by addition of 0.2 ml of 0.2 N perchloric acid containing 0.5 mM sodium bisulfite and dihydroxybenzylamine, and the tubes were centrifuged. The evaluation of the amounts of L-dopa formed was carried out in the HPLC system in a similar way to the CA analysis described above. Details concerning the analysis of TH activity have been previously reported (12). Activity of TH was expressed as ng of L-dopa formed/mg of tissue weight/hour of incubation.

Plasma Hormone Determinations

Plasma PRL, ACTH and corticosterone levels were measured by specific antibody radioimmunoassays. Prolactin was analyzed with a double antibody radioimmunoassay, using materials kindly supplied by the NIADDK. The intraassay coefficient of variation was 3.8%, the interassay coefficient of variation was 8% and the sensitivity was 0.05 ng/tube when rPRL-RP3 was used as standard. Plasma PRL levels were expressed as ng/ml of rPRL-RP3. Plasma ACTH levels were analyzed using antiserum generated in rabbit against human ACTH-(1–24) (IgG-ACTH-1, IgG Corp., Nashville, TN). Iodinated ACTH was obtained from Radioassay Systems Laboratories (Carson, CA). The intra- and interassay coefficients of variation were 4.5% and 10.1%, respectively, whereas the minimum detectable dose was 0.5 pg/tube. Plasma ACTH levels were expressed as pg/ml. Plasma corticosterone levels were measured after previous extraction into methylene chloride using antiserum 337 obtained as a gift from Dr. G. Niswender (Colorado State University). [^{125}I]-corticosterone was obtained from Amersham, Inc. (Chicago, IL). The intra- and interassay coefficients of variation were 5.1% and 12.5%, respectively, whereas the minimum detectable dose was 7 pg/tube. Plasma corticosterone levels were expressed as ng/ml. Details concerning PRL, ACTH and corticosterone radioimmunoassay methods have been previously published (8,31).

Plasma THC Determination

Plasma THC levels were analyzed using a specific RIA kit prepared at the Research Triangle Institute (Research Triangle Park, NC) and furnished by National Institute of Drug Abuse. Sample volumes of 100 μl were extracted with methanol. The antiserum was generated against Δ^9-THC; the radioligand was ^{125}I-Δ^8-THC. The reference preparation was Δ^9-THC in human plasma. The assay readable range was 1–100 ng/ml (3.18–318 nM) (23). Plasma THC levels were expressed as ng/ml.

Statistics

All data were tested for normality of distribution by the Kolmogorov-Smirnov test. A multiple comparison among the three treatments for each time was made using either one-way analysis of variance for normal distributions or Kruskal-Wallis test for nonhomogeneous distributions. Analysis of statistical correlations for individual values among different parameters was also made in some cases. Differences were considered significant if the probability of error was less than 5%.

RESULTS

Effects of THC on Adrenal Medullary Function

Acute exposure to THC caused a significant decrease in the adrenal medulla contents of both NE and E (Fig. 1). These decreases were mainly manifested after treatment with the highest dose of THC and were not accompanied by a statistically significant decrease in adrenal medullary TH activity (Fig. 1). However, the high dose of THC produced a significant increase in the E/NE ratio (Fig. 1), which may be used as an indirect indication of the activity of phenylethanolamine-N-methyl transferase, the enzyme involved in the synthesis of E from NE.

These acute effects disappeared after seven or fourteen days of a daily treatment with THC (Figs. 2 and 3), which suggests the possible development of tolerance to the drug. This could be related to a possible increase in the THC metabolism after subchronic and chronic treatments. In support of this possibility, plasma THC levels corresponding to the same dose in these treatments were lower than those measured after an acute administration (Table 1).

No significant changes were seen in the adrenal medulla weights after THC treatment, except for a small, but significant,

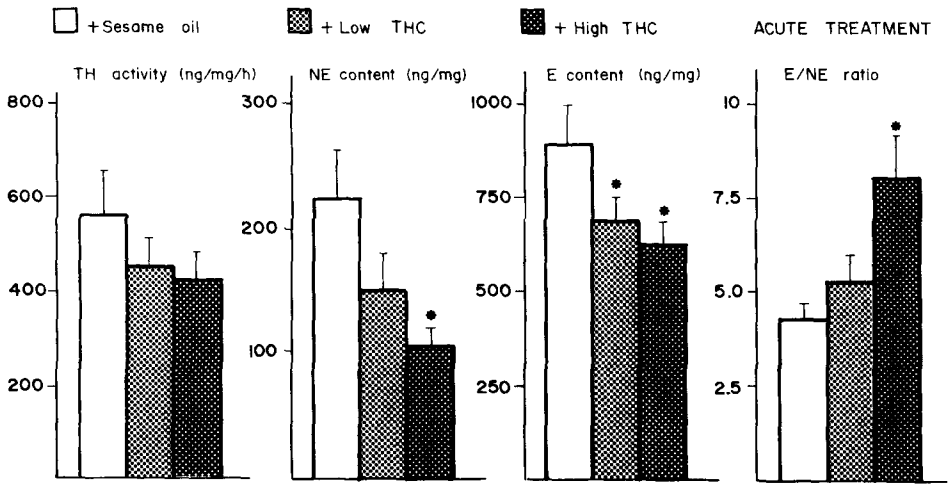

FIG. 1. Adrenomedullary tyrosine hydroxylase (TH) activity and norepinephrine (NE) and epinephrine (E) contents in male rats after acute treatment with either a low (0.5 mg/kg body weight) or a high (5 mg/kg body weight) dose of delta-9-tetrahydrocannabinol (THC). Details in the text. Values are means ± SEM of 8 per group. Statistical differences were assessed by one-way analysis of variance (*$p<0.05$).

increase in the relative adrenal medulla weight in animals exposed to the high dose of THC in the chronic study (Table 2).

Effects of THC on Plasma ACTH, PRL and Corticosterone Levels

In order to examine whether the cannabinoid effects on adrenal medullary function could be correlated to their effects on the secretion of several pituitary and corticoadrenal hormones, which could indicate a possible mediation of these hormones, we analyzed their plasma levels in the animals exposed to THC in the three different treatment conditions. Plasma PRL levels decreased after an acute exposure with the high dose of THC (Table 3), disappearing in subchronic and chronic treatments (Table 3). This decrease statistically correlated to the decreases in adrenal medullary contents of both CAs after acute THC exposure, and also to TH values (Table 4), suggesting they could be related effects. However, there was not any statistical correlation between these adrenal parameters and the plasma levels of either ACTH or corticosterone (Table 4), in spite of that the low dose of THC slightly decreased ACTH levels in the acute treatment (Table 3), and that corticosterone levels increased after an acute treatment with the high dose of this cannabinoid (Table 3).

DISCUSSION

Our results show a significant reduction in the adrenal medullary contents of both CAs after an acute exposure to THC, es-

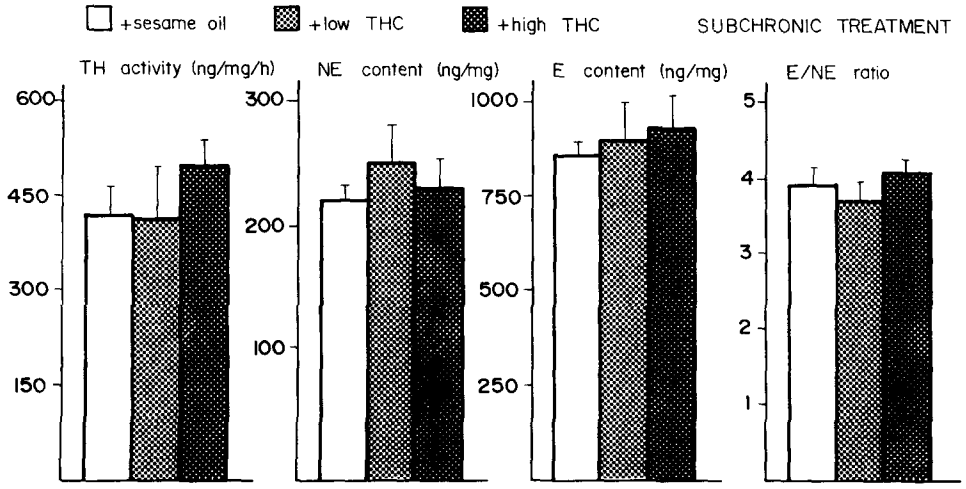

FIG. 2. Adrenomedullary tyrosine hydroxylase (TH) activity and norepinephrine (NE) and epinephrine (E) contents in male rats after a subchronic (7 days) treatment with either a low (0.5 mg/kg body weight/day) or a high (5 mg/kg body weight/day) dose of delta-9-tetrahydrocannabinol (THC). Details in the text. Values are means ± SEM of 8 determinations per group. Statistical differences were assessed by one-way analysis of variance.

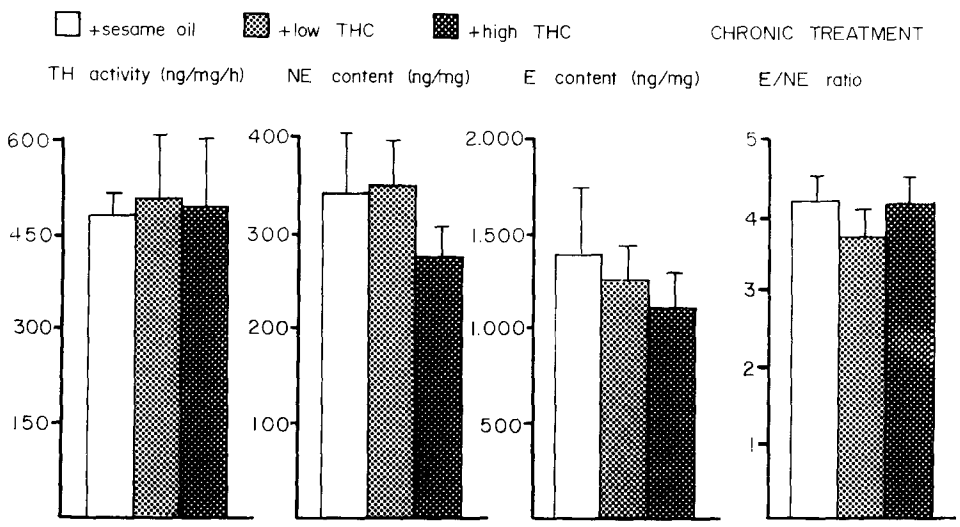

FIG. 3. Adrenomedullary tyrosine hydroxylase (TH) activity and norepinephrine (NE) and epinephrine (E) contents in male rats after a chronic (14 days) treatment with either a low (0.5 mg/kg body weight/day) or a high (5 mg/kg body weight/day) dose of delta-9-tetrahydrocannabinol (THC). Details in the text. Values are means ± SEM of 9 determinations per group. Statistical differences were assessed by one-way analysis of variance.

pecially with the high dose of this cannabinoid. This reduction in CA contents could presumably indicate an inhibitory influence of THC on CA storage. Such an effect could conceivably diminish the ability of the adrenal medulla to respond to stress situations. We suppose that this decrease was mainly originated by a mechanism, i.e., increased endogenous metabolism, other than a reduction in the capacity of the adrenal medulla to synthetize CAs, because we only observed a nonsignificant trend for a dose-related fall in adrenal medullary activity of TH after acute THC.

Although the adrenal medullary activity of phenylethanolamine-N-methyl transferase, the enzyme involved in E synthesis from NE, was not measured in this work, it is of interest to note that the E/NE ratio was significantly increased after an acute treatment with the high dose of THC. This could be considered as an indication that the activity of this enzyme may have been increased by THC.

TABLE 1

PLASMA THC LEVELS

Treatment	Treatments		
	+ Oil	+ Low THC	+ High THC
Acute	ND[a]*	25.24 ± 3.23[b]	73.73 ± 13.68[c]
Subchronic	ND[a]*	22.14 ± 1.62[b]	38.80 ± 3.30[c]
Chronic	ND[a]*	17.50 ± 2.84[b]	41.07 ± 4.58[c]

Values with a different letter are statistically different.

*<1 ng/ml.

Plasma delta-9-tetrahydrocannabinol (THC) levels (ng/ml) in male rats after acute, subchronic (7 days) and chronic (14 days) treatments with either a low (0.5 mg/kg body weight/day) or a high (5 mg/kg body weight/day) dose of this cannabinoid. Details in the text. Values are means ± SEM. N = 8 animals per group was used for acute and subchronic experiments and N = 9 for chronic experiment. Statistical differences among the three different treatments for each time were assessed by one-way analysis of variance.

This inhibitory effect of THC on CA storage observed in our study agrees with previous observations of other authors. Acute administration of THC did not alter plasma CA levels in male rats (29), but CAs were decreased after a prolonged treatment (28,29) indicating a reduced sympatho-adrenomedullary responsiveness in these animals. Moreover, it has been shown that THC has a transient stimulatory effect followed by a prolonged inhibitory action on the production of CAs by the adrenal medulla (25). These effects are consistent with bradycardia, decreased cardiac output and other autonomic effects of THC exposure (14,23), and support a possible inhibitory action of THC on adrenal medullary function.

It is important to note that these effects of THC on adrenal

TABLE 2

ADRENAL MEDULLA WEIGHT

Parameters	Treatments		
	+ Oil	+ Low THC	+ High THC
Adrenal Medulla Weight (mg):			
Acute	23.60 ± 1.15	25.36 ± 0.89	26.26 ± 1.02
Subchronic	28.55 ± 0.79	27.85 ± 1.35	29.14 ± 1.30
Chronic	30.20 ± 0.98	28.94 ± 1.16	32.95 ± 1.46
Adrenal Medulla Weight/Body Weight (mg/g):			
Acute	0.096 ± 0.004	0.102 ± 0.003	0.106 ± 0.004
Subchronic	0.096 ± 0.004	0.094 ± 0.005	0.105 ± 0.005
Chronic	0.090 ± 0.003	0.090 ± 0.003	0.106 ± 0.007*

*$p<0.05$ versus the respective oil-fed group.

Absolute and relative (per body weight) adrenal medulla weights in male rats after acute, subchronic (7 days) and chronic (14 days) treatments with either a low (0.5 mg/kg body weight/day) or a high (5 mg/kg body weight/day) dose of delta-9-tetrahydrocannabinol (THC). Details in the text. Values are means ± SEM. N = 8 animals per group was used for acute and subchronic experiments and N = 9 for chronic experiment. Statistical differences among the three different treatments for each time were assessed by one-way analysis of variance.

TABLE 3

PLASMA PRL, ACTH AND CORTICOSTERONE LEVELS

Parameters	Treatments + Oil	+ Low THC	+ High THC
PRL (ng/ml):			
Acute	16.75 ± 3.90[a]	10.03 ± 2.09[a]	5.13 ± 0.24[b]
Subchronic	7.44 ± 0.62[a]	7.51 ± 0.85[a]	5.73 ± 0.84[a]
Chronic	6.68 ± 0.45[a]	6.31 ± 0.83[a]	5.73 ± 0.24[a]
ACTH (pg/ml):			
Acute	50.96 ± 8.36[x]	33.17 ± 2.58[y]	51.90 ± 8.32[x]
Subchronic	41.86 ± 3.50[x]	40.09 ± 4.54[x]	61.39 ± 13.93[x]
Chronic	46.26 ± 4.84[a]	47.47 ± 4.71[a]	39.33 ± 3.29[a]
Corticosterone (ng/ml):			
Acute	8.56 ± 2.27[x]	14.44 ± 6.71[x]	139.53 ± 56.38[y]
Subchronic	9.41 ± 3.51[x]	6.00 ± 1.11[x]	18.73 ± 5.40[x]
Chronic	11.18 ± 2.39[a]	17.46 ± 4.21[a]	18.67 ± 4.31[a]

Values with a different letter are statistically different (a,b notation was used for ANOVA and x,y notation for Kruskal-Wallis test).

Plasma PRL, ACTH, corticosterone levels in male rats after acute, subchronic (7 days) and chronic (14 days) treatments with either a low (0.5 mg/kg body weight/day) or a high (5 mg/kg body weight/day) dose of delta-9-tetrahydrocannabinol (THC). Details in the text. Values are means ± SEM. N=8 animals per group was used for acute and subchronic experiments and N=9 for chronic experiment. Statistical differences among the three different treatments for each time were assessed by one-way analysis of variance or Kruskal-Wallis test as required.

TABLE 4

STATISTICAL CORRELATIONS

Parameters	r	*p* Value
NE		
PRL	+.42593	F(3,989)0.06114
ACTH	−.3053	F(1,747)0.20377
Corticosterone	−.2808	F(1,540)0.23048
E		
PRL	+.49362	F(5,799)0.0270
ACTH	−.1854	F(0,605)0.447
Corticosterone	−.0992	F(0,179)0.67748
TH		
PRL	+.5679	F(8,570)0.00899
ACTH	−.0885	F(0,134)0.7188
Corticosterone	−.0596	F(0,064)0.8030

Statistical correlations (r values) among adrenal medullary parameters (catecholamine contents and tyrosine hydroxylase activity) and plasma PRL, ACTH and corticosterone levels in male rats after an acute treatment with either a low (0.5 mg/kg body weight/day) or a high (5 mg/kg body weight/day) dose of delta-9-tetrahydrocannabinol (THC). Details in the text. Statistical differences were assessed by one-way analysis of variance.

medullary function appeared only after an acute exposure to this cannabinoid and disappeared after seven or fourteen days of a daily treatment with THC. This suggests development of tolerance to this drug, as indicated by its effects on other functions (4, 6, 23). It is likely that this was related to a possible increase in the THC peripheral metabolism, leading to an increased plasma clearance, in subchronic and chronic situations. This suggestion is supported by the observation that plasma THC levels in subchronic and chronic situations were lower than those measured after an acute administration.

Secretion of PRL, ACTH and corticosterone can be affected by the exposure to cannabinoids (2, 4, 7, 16, 18, 20, 21, 24, 30) and each of the hormones is involved in the regulation of the adrenal medullary function (3, 11, 24, 32). However, measurements of plasma ACTH and corticosterone levels suggest that neither the acute effects of THC on the adrenal medulla nor the development of tolerance observed in the present study were mediated by changes in the secretion of these hormones. Acute administration of a high dose of THC produced a very pronounced increase in corticosterone levels. This effect disappeared after one or two weeks of THC treatment, as shown by others (21). Surprisingly, the changes in corticosterone were not correlated with changes in ACTH levels, which were decreased after acute exposure with the low dose of THC. This could indicate involvement of different mechanisms for these effects, perhaps centrally mediated for ACTH and peripherally mediated for corticosterone.

However, there was parallelism between the adverse effects of acute THC on PRL levels, they decreased after an acute THC exposure but returned to control values after prolonged treatment, and the reduction in CA stores. The statistical analysis of these parameters revealed a slight, although significant, degree of correlation, which could support a possible mediation of PRL in acute effects of THC on adrenal medullary CAs. However, the possibility that THC may have acted directly on the adrenal medullary cells, mainly chromaffin cells, should be also considered. In this context, it may be pertinent that the existence of at least two types of cannabinoid binding sites has been recently reported in the brain (5,27). These receptors have been characterized in brain areas (5) and in cultured neuronal cell lines (15). It is interesting to consider the possibility that these binding sites may also be present in the chromaffin cells, which have the same embryonic origin as the neuronal cells.

In summary, acute exposure to THC caused an alteration in adrenal medullary function, reflected by a decrease in the endogenous stores of both CAs, which could influence the adrenal response to stress situations. However, this effect disappeared after chronic THC treatment, suggesting the development of tolerance to this drug. The mechanism(s) involved in this effect is still unknown, although both a possible mediation of changes in PRL release and a direct effect on adrenal medullary cells can be considered.

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