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Interaction of Δ^9-Tetrahydrocannabinol with Reserpine, Phenobarbital, and LSD-25 on Plasma and Adrenal Corticosterone

G. MITRA, M. K. PODDAR, AND J. J. GHOSH[1]

Department of Biochemistry, Calcutta University, Calcutta-700019, India

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Interaction of Δ^9-Tetrahydrocannabinol with Reserpine, Phenobarbital, and LSD-25 on Plasma and Adrenal Corticosterone. MITRA, G., PODDAR, M. K., AND GHOSH, J. J. (1977). *Toxicol. Appl. Pharmacol.* **42**, 505–512. Δ^9-Tetrahydrocannabinol (Δ^9-THC; 10 and 50 mg/kg) administered acutely produces significant hypersecretion of corticosterone. Phenobarbital (75 mg/kg) administration lowers the basal corticosterone concentrations and partially inhibits the corticosterone elevating effect of Δ^9-THC (10 mg/kg). LSD-25 (50 μg/kg) produces neither a stimulatory nor an inhibitory effect on Δ^9-THC-induced changes and does not affect the corticosterone concentrations. Administration of reserpine (2.5 mg/kg) produces a significant elevation of corticosterone and an additive effect on the Δ^9-THC (10 mg/kg)-induced changes upon simultaneous administration of the two drugs. No tolerance to the corticosterone elevating effect of Δ^9-THC is obtained upon chronic administration (10 mg/kg/day for 21 days). Rats treated chronically with Δ^9-THC respond to one single dose of the above drugs in a way similar to that observed in acute studies.

Δ^9-Tetrahydrocannabinol (Δ^9-THC) has been reported by various investigators to cause changes in adrenocortical activities (Dewey *et al.*, 1970; Poddar and Ghosh, 1972; Biswas and Ghosh, 1976). In eliciting responses by Δ^9-THC, the involvement of the adenohypophysis and hypothalamus, rather than the adrenal cortex, has been implied, and its mode of action has been found to differ from those of narcotic analgesics (Kubena *et al.*, 1971; Ling *et al.*, 1973; Dewey *et al.*, 1970). There are also reports of Δ^9-THC interactions with other psychotropic drugs which influence the behavioral and pharmacological responses elicited by Δ^9-THC (Garriot *et al.*, 1967; Kubena and Barry, 1970; Mitra *et al.*, 1975). Hence, for a better understanding of the psychopharmacological mode of action of Δ^9-THC, the knowledge of its interaction with other psychotropic drugs at the neuroendocrine level may be helpful. The present investigation deals with the effects of interaction of Δ^9-THC and other psychotropic agents, such as reserpine, phenobarbital, and LSD-25 in rats.

METHODS

Male albino rats of the Charles River strain (120–150 g) were housed in groups of six to eight in large wire cages (20 × 15 cm) with food and water *ad libitum*. The animal quarters were maintained on a cycle of 12-hr light (6:00 AM to 6:00 PM) and 12-hr dark.

[1] To whom all correspondence should be sent at: University of Calcutta, 35 Ballygunge Circular Road, Calcutta-700019, India.

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Δ^9-Tetrahydrocannabinol (98% purity), containing 1.18% Δ^8-THC and 0.6% cannabinol as impurities, was obtained from the United Nations, Narcotics Division, Geneva. Phenobarbital sodium was obtained from May & Baker (India) Private, Ltd.; reserpine was from CIBA of India, Ltd.; and LSD-25 was from Sandoz, Switzerland.

For acute studies rats were divided into nine groups. Just prior to ip administration of each of the psychotropic agents, i.e., reserpine or phenobarbital or LSD-25, Δ^9-THC (suspended in saline containing 1% Tween-80) in a volume of 0.5 ml/100 g was given ip Vehicles corresponding to each group were given to control animals. The rats were sacrificed by decapitation 45, 90, 180, and 360 min after the last injection. For

TABLE 1

INTERACTION OF Δ^9-THC WITH RESERPINE, PHENOBARBITAL, AND LSD DRUG TREATMENT SCHEDULE IN RATS

Acute[a]			Subchronic[b]		
Group	Treatment	Dose	Group	Treatment	Dose
1	Saline–Tween 80	—	1	Saline–Tween 80	—
2	Δ^9-THC	10 mg/kg	2	Δ^9-THC (21 days)	10 mg/kg/day
3	Δ^9-THC	50 mg/kg	3	+reserpine	+2.5 mg/kg
4	Phenobarbital	75 mg/kg	4	+phenobarbital	+75 mg/kg
5	Phenobarbital + Δ^9-THC	75 + 10 mg/kg	5	LSD-25	+50 μg/kg
6	Reserpine	2.5 mg/kg			
7	Reserpine + Δ^9-THC	2.5 + 10 mg/kg			
8	LSD-25	50 μg/kg			
9	LSD-25 + Δ^9-THC	50 μg/kg + 10 mg/kg			

[a] Rats were sacrificed 45, 90, 180, and 360 min after the last injection.
[b] Rats of groups 1 and 2 were sacrificed 45, 90, 180, and 360 min after the last injection, and those of groups 3–5 were sacrificed 360 min after the last injection.

subchronic studies, animals received Δ^9-THC (10 mg/kg/day) for 21 days (ip). Animals of the control groups were treated with the vehicle. The animals of both groups were sacrificed 45, 90, 180, and 360 min after the last injection. The other groups of animals received Δ^9-THC (10 mg/kg/day) for 21 consecutive days and a single dose of either reserpine, phenobarbital, or LSD-25 on the twenty-first day along with the last injection of Δ^9-THC. The animals were sacrificed 360 min after the last injection. Injections were scheduled so that all animals could be sacrificed at a specified time of the day (3:30 to 4:30 PM) in order to avoid any effect of circadian variations. Details of drug treatment are summarized in Table 1.

Immediately after sacrifice, trunk blood was collected in heparinized tubes, and the adrenals were removed. Plasma was prepared by centrifugation in the cold within 10 min, and adrenals were freed from the adhering tissue, weighed, and kept in the cold. Spectrophotoflurometric assay of plasma and adrenal corticosterone was done according to the methods of Purves and Sirret (1965) and Vernikoss-Daniellis *et al.* (1966), respectively.

RESULTS AND DISCUSSION

The results of the present study indicate that Δ^9-THC produces an acute stimulation of ACTH release as measured by a marked elevation of the concentration of plasma and adrenal corticosterone. The response to a dose of 50 mg/kg was greater than that obtained with a dose of 10 mg/kg (Tables 2 and 3). The peak steroid response in both plasma and adrenals following acute administration of Δ^9-THC occurs within 45–90 min and then gradually declines. The plasma corticosterone concentration returned nearly to the basal level 6 hr after the Δ^9-THC administration. The present results

TABLE 2

EFFECT OF ACUTE ADMINISTRATION OF RESERPINE, PHENOBARBITAL, AND LSD-25 ON Δ^9-THC-INDUCED CHANGES OF PLASMA CORTICOSTERONE CONCENTRATIONS IN THE RAT

Treatment	Plasma corticosterone concentration (μg/100 ml)			
	45 min	90 min	180 min	360 min
Control (saline–Tween 80)	15.03 ± 1.50[a]	17.71 ± 1.35	16.10 ± 1.23	15.88 ± 1.4
Δ^9-THC (10 mg/kg)	41.23 ± 4.01[b]	47.52 ± 3.98[b]	33.01 ± 3.52[b]	20.52 ± 1.62[c]
Δ^9-THC (50 mg/kg)	52.65 ± 3.57[b]	58.15 ± 2.85[b]	41.45 ± 2.86[b]	22.15 ± 2.08[d]
Phenobarbital (75 mg/kg)	15.96 ± 1.25	12.40 ± 1.28	9.71 ± 1.02[b]	13.00 ± 1.28
Phenobarbital (75 mg/kg) + Δ^9-THC (10 mg/kg)	34.13 ± 1.98[b]	36.62 ± 2.05[b]	25.24 ± 1.28[d]	16.60 ± 1.46
Reserpine (2.5 mg/kg)	37.64 ± 4.60[b]	45.28 ± 4.25[b]	39.24 ± 3.28[b]	38.34 ± 4.15[b]
Reserpine (2.5 mg/kg) + Δ^9-THC (10 mg/kg)	54.00 ± 4.88[b]	52.19 ± 5.08[b]	45.20 ± 3.92[b]	35.92 ± 3.75[b]
LSD-25 (50 μg/kg)	15.75 ± 1.32	16.70 ± 1.54	22.70 ± 2.31[d]	17.40 ± 1.48
LSD-25 (50 μg/kg) + Δ^9-THC (10 mg/kg)	37.80 ± 4.31[b]	45.10 ± 4.82[b]	30.20 ± 3.09[b]	17.50 ± 1.42

[a] Values are expressed as mean ± SE of three different sets of experiments. Number of rats used was four in each group.
[b] Differs from control value, $p < 0.001$, Student's t test.
[c] Differs from control value, $p < 0.005$, Student's t test.
[d] Differs from control value, $p < 0.01$, Student's t test.

corroborate the earlier observations that Δ^9-THC produces a significant stimulation of the pituitary–adrenal axis.

The results shown in Tables 2 and 3 indicate that phenobarbital administration (75 mg/kg) moderately decreased the basal corticosterone concentrations. Upon simultaneous acute administration of phenobarbital and Δ^9-THC, a partial inhibition of the corticosterone elevating effect of Δ^9-THC was found. Barbiturates have been reported to inhibit the release of ACTH following various stressful stimuli, and a combination of pentobarbital sodium and morphine sulfate has been shown to block the pituitary–adrenal activation following Δ^9-THC administration (Szot and Murphy, 1970; Kubena *et al.*, 1971). It has been reported (Gold and Ganong, 1967) that phenobarbital does not interfere with ACTH-stimulated release of corticosterone from the adrenal, whereas the ACTH-suppressing action of barbiturates following certain stressful stimuli is apparently due to depression of the reticular activating system which thereby prevents

the stimulatory impulses from reaching the hypothalamus. Hence, the present results suggest that phenobarbital changes the Δ^9-THC action by altering the sensitivity of the CNS, thereby causing a partial inhibition of Δ^9-THC induced release of the corticotropic releasing factor (CRF) from the hypothalamus. This hypothesis is in agreement with the contention of Kubena and Barry (1970) that the interaction between barbiturates and Δ^9-THC is at the CNS level.

From the present study it is also apparent that LSD-25, another psychotomimetic drug, at a dose of 50 μg/kg, has neither an inhibitory nor a stimulatory effect on ACTH release, as is evident from the almost unchanged corticosterone value following

TABLE 3

EFFECT OF ACUTE ADMINISTRATION OF RESERPINE, PHENOBARBITAL AND LSD-25 ON Δ^9-THC-INDUCED CHANGES OF ADRENAL CORTICOSTERONE CONCENTRATIONS IN THE RAT

Treatment	Adrenal corticosterone concentration (μg/g of wet tissue)			
	45 min	90 min	180 min	360 min
Control (saline–Tween 80)	4.90 ± 0.72[a]	4.91 ± 0.74	5.08 ± 81.0	4.51 ± 0.32
Δ^9-THC (10 mg/kg)	11.34 ± 1.28[b]	10.12 ± 0.82[b]	8.30 ± 1.25[c]	6.31 ± 0.46[d]
Δ^9-THC (10 mg/kg)	14.08 ± 0.93[b]	13.59 ± 1.46[b]	11.78 ± 0.77[b]	6.58 ± 0.32[b]
Phenobarbital (75 mg/kg)	4.38 ± 0.55	3.03 ± 0.37[c]	2.62 ± 0.43[e]	3.71 ± 0.61
Phenobarbital (75 mg/kg) + Δ^9-THC (10 mg/kg)	10.30 ± 0.98[b]	7.14 ± 0.92[e]	6.50 ± 0.48	4.68 ± 0.56
Reserpine (2.5 mg/kg)	9.73 ± 1.08[d]	8.95 ± 0.52[b]	10.00 ± 0.92[b]	9.12 ± 1.21[d]
Reserpine (2.5 mg/kg) + Δ^9-THC (10 mg/kg)	12.48 ± 0.78[b]	13.07 ± 0.71[b]	11.32 ± 1.01[b]	9.25 ± 1.08[b]
LSD-25 (50 μg/kg)	5.32 ± 0.48	5.01 ± 0.79	6.12 ± 0.92	4.90 ± 0.58
LSD 25 (50 μg/kg) + Δ^9-THC (10 mg/kg)	9.48 ± 0.72[b]	10.02 ± 1.20[d]	8.47 ± 0.94[e]	5.89 ± 0.61

[a] Values are expressed as mean ± SE of three different sets of experiments.
[b] Differs from control value, $p < 0.001$, Student's t test.
[c] Differs from control value, $p < 0.05$, Student's t test.
[d] Differs from control value, $p < 0.005$, Student's t test.
[e] Differs from control value, $p < 0.01$, Student's t test.

administration of this drug (Tables 2 and 3). Furthermore, upon simultaneous administration with Δ^9-THC, it neither potentiated nor inhibited the Δ^9-THC-induced changes in corticosterone concentrations. These results support the earlier observations that administration of LSD causes no increase in urinary 17-hydroxy corticosteroid excretion (Nadel *et al.*, 1957) and that it does not affect the adrenal responsiveness to ACTH or sensitivity of the pituitary–adrenal axis to stress (Ganong *et al.*, 1961).

Reserpine, a well-known stimulator of the pituitary–adrenal axis, produced a significant elevation of both plasma and adrenal corticosterone concentrations, and the duration of the corticosterone response remained undiminished up to 6 hr. The present result suggests that, although there is evidence of intense hypothalamic stimulation leading to ACTH release following both Δ^9-THC and reserpine, the duration of ACTH secretion evoked by Δ^9-THC is less than that observed after reserpine treatment. Upon simultaneous administration of Δ^9-THC (10 mg/kg) and reserpine (2.5 mg/kg), the

response in corticosterone concentrations was greater than that due to either of the drugs alone, and the duration of ACTH release also increased in comparison to the effects of Δ^9-THC alone. These results indicate an additive effect of reserpine on Δ^9-THC-induced action at the level of the pituitary–adrenal axis, which may be due either to additional release of ACTH or to increased corticosteroid output. It has been postulated by several investigators that reserpine activates CRF release by depleting or antagonizing biogenic amines which act as inhibitory neurotransmitters (Marks *et al.*, 1970; Ganong and Lorenz, 1967), since this drug causes a marked depletion of both serotonin and noradrenaline in brain, and, conversely, certain monoamine oxidase inhibitors increase hypothalamic serotonin and noradrenaline concentrations and block ACTH secretion (Tullner and Hertz, 1964; Ganong *et al.*, 1965). Additive effects of reserpine on Δ^9-THC-induced action as observed in the present study indicate the possible potentiation may be at this level. It has been reported (Holtzman *et al.*, 1969;

TABLE 4

EFFECT OF SUBCHRONIC ADMINISTRATION OF Δ^9-THC ON PLASMA AND ADRENAL CORTICOSTERONE CONCENTRATIONS IN THE RAT

Time after Δ^9-THC (min)	Plasma corticosterone (μg/100 ml)		Adrenal corticosterone (μg/g of wet tissue)	
	Control (saline–Tween 80)	Δ^9-THC (10 mg/kg/day)	Control (saline–Tween 80)	Δ^9-THC (10 mg/kg/day)
45	16.25 ± 1.26[a]	37.95 ± 1.95[b]	4.88 ± 0.76	9.03 ± 0.98[c]
90	16.60 ± 1.82	29.94 ± 2.46[b]	4.24 ± 0.70	7.99 ± 1.20[d]
180	13.30 ± 1.58	24.46 ± 2.17[b]	4.00 ± 0.52	6.92 ± 0.82[c]
360	16.43 ± 1.75	15.98 ± 1.64	4.62 ± 0.78	6.03 ± 0.92

[a] Values are expressed as mean ± SE of three different sets of experiments. Number of rats used was four in each group.
[b] Differs from control value, $p < 0.001$, Student's t test.
[c] Differs from control value, $p < 0.005$, Student's t test.
[d] Differs from control value, $p < 0.01$, Student's t test.

Poddar and Ghosh, 1976; Graham *et al.*, 1974) that, after Δ^9-THC administration, the endogenous noradrenaline content of the brain decreases, and Δ^9-THC administration causes an accelerated rate of disappearance of intracisternally administered noradrenaline (Schildkraut and Efron, 1971). Hence, it may be speculated that Δ^9-THC, like reserpine, presumably acts in the catecholaminergic neural system by counteracting the effect of an inhibitory neurotransmitter which normally reduces the CRF output.

From the results of the present study (Table 4) it appears that, even after daily administration of Δ^9-THC (10 mg/kg) for 21 consecutive days, there is still a significant elevation of plasma corticosterone, although these values decline at a quicker rate than those observed after a single injection of Δ^9-THC (Table 2). This indicates that the capacity of the animals to stimulate corticosterone release was not significantly altered even after administration of Δ^9-THC for 21 days, although this response appeared to be somewhat diminished when compared to that of the acute groups. These results are also consistent with the observations of Kubena and Barry (1970) and Kokka and Garcia (1974).

Results of interaction studies after the administration of a single dose of reserpine (2.5 mg/kg) in the subchronic Δ^9-THC (10 mg/kg day for 21 days)-treated rats (Table 5) showed that, after 21 days, Δ^9-THC-treated rats responded to one challenging dose of reserpine in a way similar to that observed in the acute studies. A significant elevation of corticosterone values has been observed even after 6 hr. This indicates that the pituitary store of ACTH in animals treated with Δ^9-THC for 21 days is not totally exhausted, and hence another stress can produce additional ACTH release and corticosterone output from the adrenal cortex. Phenobarbital (75 mg/kg) and LSD-25 (50 μg/kg) under similar conditions also produce a type of response in Δ^9-THC treated (21 days) animals similar to that observed after acute administration. Hence, it can be said that, under

TABLE 5

EFFECT OF INTERACTION OF Δ^9-THC WITH RESERPINE, PHENOBARBITAL, AND LSD-25 ON THE PLASMA AND ADRENAL CORTICOSTERONE CONCENTRATIONS UNDER SUBCHRONIC CONDITIONS[a]

Treatment	Corticosterone	
	Plasma (μg/100 ml)	Adrenal (μg/g of wet tissue)
Control (saline–Tween 80)	14.40 ± 1.11[b]	4.86 ± 0.55
Δ^9-THC (10mg/kg/day)		
+ Reserpine (2.5 mg/kg)	31.18 ± 3.48[c]	8.32 ± 0.71[d]
+ Phenobarbital (75 mg/kg)	13.30 ± 1.25	5.29 ± 0.15
+ LSD-25 (50 μg/kg)	15.02 ± 2.05	6.18 ± 0.91

[a] Rats were treated with Δ^9-THC (10mg/kg/day) for 21 days, and a single dose of either reserpine, phenobarbital, or LSD-25 at their respective doses was given along with the last injection of Δ^9-THC.

[b] Values are expressed as mean ± SE of three different sets of experiments. Number of rats was four in each group.

[c] Differs from control value, $p < 0.001$, Student's t test.

[d] Differs from control value, $p < 0.005$, Student's t test.

these experimental conditions, the response of the pituitary–adrenal system to Δ^9-THC appears to be different from that reported for morphine, reserpine, and chlorpromazine (Wells *et al.*, 1956; Ashford and Shapero, 1962; Briggs and Munson, 1955). The latter agents, which after acute injection produce increased ACTH secretion, have been reported to inhibit the response to subsequent stresses in the rat. This discrepancy may be related to the fact that duration of corticosterone response following a single injection of Δ^9-THC is only 8 hr (Kubena and Barry, 1970). On the other hand, following a single dose of reserpine, plasma concentration of corticosterone remains elevated for as long as 24 hr (Montanari and Stockham, 1962). These results support the view that the rate of pituitary–adrenal adaptation to the corticosteroid stimulating drug is dependent upon the duration of ACTH hypersecretion caused by the drug (Ellis, 1966).

It is apparent from the present study that different psychoactive agents affect the corticosterone elevating effect of Δ^9-THC in a different but characteristic manner.

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