MOLECULAR PHARMACOLOGY, 26:532-538

Cannabinoid Inhibition of Adenylate Cyclase

Pharmacology of the Response in Neuroblastoma Cell Membranes

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Received April 23, 1984; Accepted July 23, 1984

SUMMARY

Adenylate cyclase in plasma membranes was inhibited by micromolar concentrations of Δ^8-tetrahydrocannabinol and Δ^9-tetrahydrocannabinol and by levonantradol and desacetyllevonantradol. This inhibition was noncompetitive for stimulation of the enzyme at the prostanoid receptor by prostaglandin E_1 or prostacyclin, or at the peptide receptor by secretin or vasoactive intestinal peptide. Forskolin-activated adenylate cyclase was also inhibited by cannabimimetic agents. Inhibition by cannabinoid compounds was neither synergistic nor additive with muscarinic or *alpha*-adrenergic agents when each was present at maximally inhibitory concentrations. Cannabinoid inhibition was not blocked by atropine, yohimbine, or naloxone, suggesting that muscarinic, *alpha*$_2$-adrenergic and certain opiate receptors may not be required for the response. The inhibition of adenylate cyclase was specific for psychoactive cannabinoids, since cannabinol and cannabidiol produced minimal or no response. Inhibition was also stereoselective, since dextronantradol did not produce the response. A biphasic log dose-response curve was observed for each of the cannabinoid drugs, such that reversal of the inhibition occurred at 3–10 μM. Possible mechanisms for the effects of cannabinoid drugs on adenylate cyclase activity are discussed.

INTRODUCTION

We recently reported that cannabinoid drugs decrease basal and prostanoid-stimulated cyclic AMP accumulation in intact neuroblastoma cells (1). This response could be attributed to an inhibition of adenylate cyclase activity in membranes derived from these cells. Inhibition was demonstrated for Δ^8-THC[1] and Δ^9-THC, the natural bioactive products in marihuana extracts, and the nantradol class of synthetic cannabimimetic analogs.

One hypothesis of cannabinoid actions is that these drugs may be active at a specific neurotransmitter receptor site. Our previous report tested the hypothesis, proposed by Milne and Johnson (2), that cannabinoid drugs may operate through a prostaglandin receptor. Adenylate cyclase activity in the N18TG2 neuroblastoma cell line is stimulated by prostacyclin and prostaglandin E_1 (3). However, in this cell system, the cannabinoid drugs failed to act as stimulatory agonists or to competitively antagonize the adenylate cyclase response to prostanoid agonists (1).

The present investigation further examines the pharmacology of the cannabinoid inhibition of adenylate cyclase in a membrane preparation from the N18TG2 clone of neuroblastoma cells. This cell line also expresses secretin receptors associated with the stimulation of adenylate cyclase (4), and *alpha*-adrenergic and muscarinic cholinergic receptors (1) associated with the inhibition of adenylate cyclase. The data suggest that cannabimimetic drugs do not inhibit adenylate cyclase by a direct interaction with either of these pharmacological receptor types.

MATERIALS AND METHODS

Adenylate cyclase determinations. A plasma membrane fraction from N18TG2 cells was prepared by differential and sucrose density gradient sedimentations and stored at −80° as previously described (1). Adenylate cyclase activity was determined in a 100-μl volume containing 50 mM Na-HEPES, pH 8.0, 1 mM EDTA, 5 mM $MgCl_2$, 100 μM GTP, 0.1 mM RO20-1724, 0.1 mg/ml bovine serum albumin, 10 μg/ml pyruvate kinase, 3.0 mM phosphoenolpyruvate, 0.5 mM ATP, and 0.5 μCi of [^{32}P] ATP, unless otherwise indicated. Additional compounds were present as described in the figure legends. The reaction was initiated by addition of 10 μg of membranes, and terminated after 20 min at 30° by the procedure of Salomon *et al.* (5). [^{32}P]Cyclic AMP was isolated from

This work was supported by National Institutes of Health Grant NS16512 and a Faculty Development Award from the Pharmaceutical Manufacturers Association Foundation.

[1] The abbreviations used are: THC, tetrahydrocannabinol; K_{act}, concentration of hormone at half-maximal activity as stimulator or inhibitor; G_s, a guanine nucleotide-binding protein complex that can interact with stimulatory receptors to ultimately increase adenylate cyclase activity; G_i, a guanine nucleotide-binding protein complex that can interact with inhibitory receptors to ultimately decrease adenylate cyclase activity; HEPES, 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid.

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sequential Dowex 50W and alumina columns (5). Data points in figures and tables are means of triplicate determinations for which the coefficients of variation were between 3–10%.

Materials. [α-^{32}P]ATP and [^{3}H]cyclic AMP were from New England Nuclear. Secretin, vasoactive intestinal peptide, prostaglandin E_1, and prostacyclin were obtained and stored as previously described (3, 4). Forskolin was purchased from Calbiochem and stored at 30 mM in 95% ethanol at −20°. Yohimbine and atropine were purchased from Aldrich and Sigma, respectively. Δ^9-THC, Δ^8-THC, cannabinol, and cannabidiol were purchased from Sigma or else obtained from the National Institute of Drug Abuse. The nantradol compounds were generous donations from Pfizer, Inc. Cannabinoid compounds were stored (10 or 30 mM) at −20° in ethanol. RO20-1724 and naloxone were gifts from Hoffman-LaRoche and Endo Laboratories, respectively.

RESULTS

Stimulatory hormone-receptor interactions. In an earlier report, it was demonstrated that cannabinoid drugs appeared to reduce the maximal stimulation of adenylate cyclase by prostaglandin E_1 and by prostacyclin (1). It was further shown that the adenylate cyclase response to secretin and to vasoactive intestinal peptide was also reduced. It was therefore of interest to determine the nature of the decreased peptide-stimulated adenylate cyclase response. The effects of cannabimimetic compounds on the stimulation of adenylate cyclase by secretin are shown in Fig. 1. By linear least squares fit analysis according to the Hill equation, the K_{act} for secretin was determined to be 36 nM and the slope factor was 0.95. This is consistent with the previously reported value (4). The K_{act} for secretin in the presence of the cannabinoid drugs was between 27 and 36 nM. The cannabinoid compounds reduced the maximal stimulation by 20% (levonantradol and Δ^8-THC) to 34% (desacetyllevonantradol). The data are consistent with a noncompetitive interaction with the secretin receptor.

Data from stimulator dose-response curves for agonists at either the prostanoid or the peptide receptor were plotted according to the Eadie-Scatchard linear transformation in Fig. 2. The maximal activities (x intercepts) were lower than control values by 8 to 28% in the presence of cannabinoid compounds. The lines generated for samples containing cannabinoid drugs were essentially parallel to control curves. This indicates a minimal or nonexistent change in affinity of hormone for either prostanoid or secretin receptors. One can conclude that the effect of cannabinoid drugs on the adenylate cyclase system occurs distal to the interaction of stimulatory hormones with their receptors.

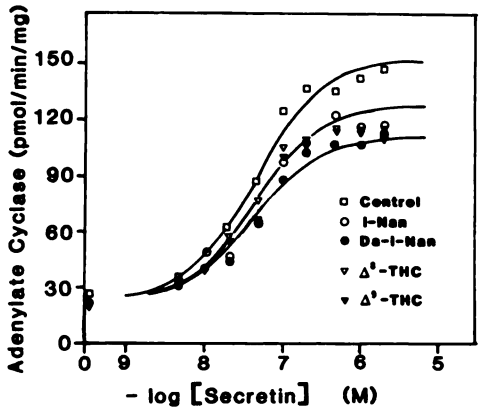

FIG. 1. *Inhibition of secretin-stimulated adenylate cyclase by cannabinoid drugs*

Adenylate cyclase activity was assayed as described in Materials and Methods except that cannabinoid drugs and GTP were present at 1 μM and $MgCl_2$ was present at 10 mM. These data are a single experiment representing four performed using these conditions. The lines are computer-generated curves, each having a slope factor of 1.00 and a K_{act} of 36 nM, but having a maximum of 100% (defined as the control peak), 80% [levonantradol (*l-Nan*), and Δ^8-THC] and 66% [desacetyllevonantradol (*Da-l-Nan*)] of control.

Inhibition of adenylate cyclase in the presence of forskolin. Forskolin is a diterpene compound that has been shown to magnify the activity of adenylate cyclase in the absence or presence of hormonal stimulators or activators (for review, see ref. 6). The site of action is believed to reside at the catalytic protein because enzymes lacking a functional G_s (S49 lymphoma cyc$^-$ variant and soluble testes enzyme) response to forskolin with an increase in activity (6). However, influences of G_s to stimulate (6) and by G_i to inhibit adenylate cyclase (7) remain intact in the presence of forskolin.

One could hypothesize that the mechanism of action of cannabinoid compounds is to block the ability of stimulatory hormones to couple to the adenylate cyclase catalytic protein via G_s. If this were true, one would predict that adenylate cyclase activity in the presence of forskolin would be altered only in response to stimulatory hormones but not in their absence. Table 1 shows that adenylate cyclase was activated synergistically by a maximal concentration of vasoactive intestinal peptide plus a submaximal concentration of forskolin. Cannabinoid drugs inhibited adenylate cyclase in the presence or absence of the stimulatory hormone. Inhibition occurred in a dose-related manner for each cannabinoid drug to about the same extent with either vasoactive intestinal peptide, forskolin, or both. These data demonstrate that cannabinoid drugs are able to inhibit adenylate cyclase effectively in the absence of a stimulatory hormone. Thus, the disruption of a stimulatory receptor-adenylate cyclase interaction is not necessarily required for cannabinoid inhibition.

Pharmacologic specificity of adenylate cyclase inhibition by cannabimimetic drugs. The interaction of cannabinoid drugs with receptors for hormones known to inhibit adenylate cyclase was investigated. Adenylate cyclase is inhibited via muscarinic and *alpha*-adrenergic receptors in the N18TG2 cell line (Table 2). The inhibition by carbachol or by epinephrine at their respective receptors is not compromised by the presence of cannabinoid drugs. Also demonstrated in Table 2, submaximal inhibition by cholinergic or adrenergic agonists could be augmented by cannabimimetic agents. However, additive inhibition was not observed when both drugs were present at their maximally inhibitory concentrations. Similar results were obtained when forskolin was present as the stimulator (data not shown).

Competitive antagonists for the muscarinic, *alpha*$_2$-adrenergic or opiate receptors failed to alter the inhibitory effects of cannabinoid drugs (Fig. 3). These drugs were present at concentrations known from previous

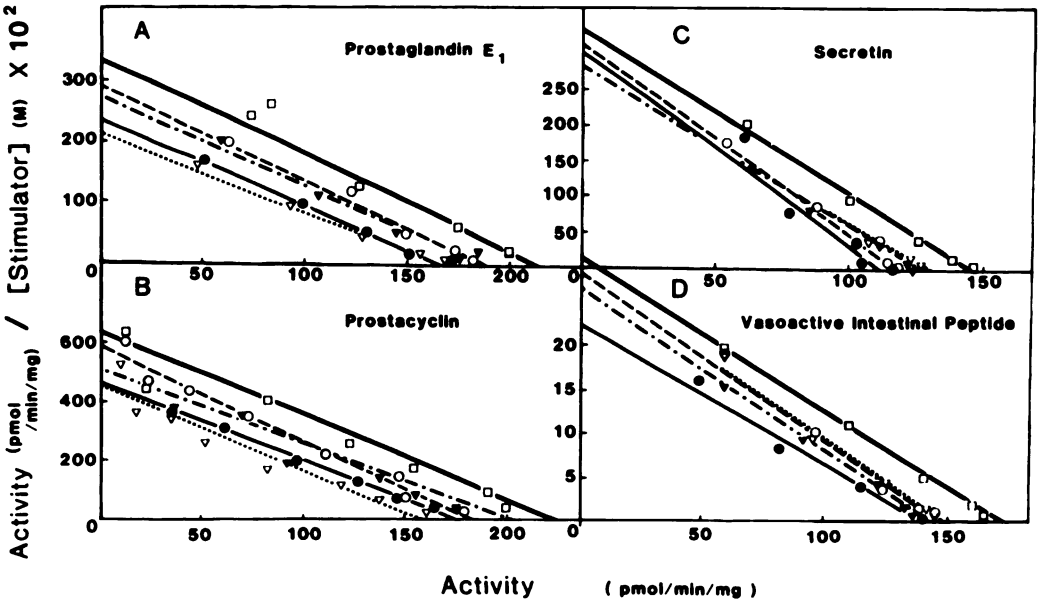

FIG. 2. *Noncompetitive inhibition of hormone-stimulated adenylate cyclase*

Eadie-Scatchard plots were constructed from single experiments in which adenylate cyclase was stimulated via the prostanoid receptor by prostaglandin E_1 (A), or prostacyclin (B), or via the peptide receptor by secretin (C), or vasoactive intestinal peptide (D). Concentrations were 1.0 μM GTP, 10 mM $MgCl_2$ and 1.0 μM cannabinoid drugs. The experiments chosen were representative of two experiments for A and D, and four experiments for B and C, using these conditions. The lines were determined by least squares fit of the points using the equation: $v/[S] = (-1/K_{act})\ v + V_{max}/K_{act}$. Vehicle only (□——□), Δ^8-THC (▽ ... ▽), Δ^9-THC (▼-·-▼), levonantradol (○– – –○), and desacetyllevonantradol (●——●).

experiments to inhibit maximally active concentrations of agonists. These results suggest that interaction with muscarinic, *alpha*$_2$-adrenergic or opiate receptors is not required for the inhibition.

Selectivity of the inhibition to cannabimimetic compounds. A log dose-response relationship could be obtained for the cannabinoid inhibition of adenylate cyclase. This is shown in Figs. 4 and 5 for secretin- and forskolin-stimulated activities, respectively. Δ^8-THC and Δ^9-THC showed very similar inhibitory potencies, being half-maximally active at about 300 nM. Cannabinol and cannabidiol, compounds reported to have limited psychoactive properties (8), produced partial inhibition at 300 nM to 3 μM.

The nantradol compounds exhibit stereospecificity both in their biological response (2, 9) and in their inhibition of adenylate cyclase (Figs. 4 and 5). Levonantradol was half-maximally active at about 100 nM. The biologically inactive stereoisomer, dextronantradol, was less potent. Desacetyllevonantradol was half-maximally active at about 10 nM, consistent with reports that this metabolic product of levonantradol is the more biologically potent compound *in vivo* (9).

Each of the cannabinoid drugs exhibited a biphasic response, peaking at 3–10 μM. Only stimulation of adenylate cyclase activity was observed with cannabidiol for secretin-stimulated activity. The most potent inhibitor of adenylate cyclase in the nantradol series studied was desacetyllevonantradol. As shown in Fig. 4, inhibition was >90% of maximal at 0.1 μM, 10- to 30-fold less than the concentration at which reversal occurred. One explanation for the apparently less efficacious inhibition by levonantradol and dextronantradol is that the stimulatory phase may begin at concentrations less than those needed for maximal inhibition. The drug concentrations at which the stimulatory phase begins may affect the maximal inhibition that can be attained with Δ^8-THC and Δ^9-THC as well.

At high drug concentrations, an influence of the ethanol solvent on adenylate cyclase becomes apparent. At ethanol concentrations exceeding 0.1%, a slight stimulation by vehicle occurred for the secretin response (Fig. 4). In contrast, ethanol produced a decrement in activity in the presence of forskolin (Fig. 5). In the latter case, the reversal portion of the cannabinoid curves was less pronounced and cannabidiol behaved as an inhibitor. Perhaps ethanol compromised adenylate cyclase in the presence of forskolin because that compound itself is very lipophilic. The effects of ethanol at higher concentrations than shown would inhibit secretin- and prostaglandin-stimulated activities as well (data not shown).

DISCUSSION

The cellular mechanism of action of cannabimimetic drugs has yet to be elucidated. A number of cellular effects of cannabinoid drugs have been observed, as reviewed by Paton (10). Three laboratories previously have reported stimulatory effects of cannabinoid drugs on cyclic AMP synthesis (11–15). In contrast, our studies in neuroblastoma cells (1) and membranes (reported here) have demonstrated a pharmacologically specific inhibition of adenylate cyclase at low concentrations of cannabimimetic agents. The reversal of this effect at higher drug concentrations may be comparable to the stimulation observed in other studies.

Dolby and Kleinsmith (11) reported that intraperito-

TABLE 1

Inhibition of forskolin-stimulated adenylate cyclase by cannabinoid drugs

Adenylate cyclase activity in membranes was determined as described in the text. Concentrations of drugs were 2 μM vasoactive intestinal peptide, 1 μM forskolin, and cannabinoid compounds as indicated. The numbers in parentheses are the percentage of adenylate cyclase activity compared with the activity in the absence of cannabinoid drugs for each group. Comparable results (not shown) are obtained in experiments in which secretin rather than vasoactive intestinal peptide is used.

Drug concentration	Adenylate cyclase		
	Vasoactive intestinal peptide	Forskolin	Vasoactive intestinal peptide plus forskolin
μM	pmol/min/mg		
Experiment 1			
Δ^6-THC			
0	160	77	456
0.1	159 (99)	78 (100)	422 (92)
1.0	134 (84)	65 (84)	356 (78)
10.0	145 (91)	67 (87)	ND[a]
Δ^9-THC			
0	164	77	435
0.1	154 (96)	79 (101)	399 (92)
1.0	136 (83)	69 (90)	400 (92)
10.0	133 (81)	62 (80)	357 (82)
Experiment 2			
Levonantradol			
0	151	123	392
0.1	144 (95)	137 (100)	359 (92)
1.0	113 (75)	98 (80)	353 (90)
10.0	108 (71)	93 (76)	312 (80)
Desacetyllevonantradol			
0	144	122	426
0.1	87 (60)	86 (70)	263 (62)
1.0	78 (54)	87 (71)	252 (59)
10.0	81 (56)	77 (63)	281 (66)

[a] ND, not determined.

TABLE 2

Interactions of cannabinoid and hormonal inhibitors of adenylate cyclase

Adenylate cyclase activity was assayed as described in Materials and Methods, with secretin (0.3 μM) present in all tubes. In A, carbachol was either absent or added at the indicated concentrations. In B, epinephrine was either absent or added at the indicated concentrations, and 100 μM ascorbate was present in all tubes. For both A and B, either vehicle (control), or 3 μM Δ^9-THC or desacetyllevonantradol was included in addition to the other components. Numbers in parentheses are the percentage of adenylate cyclase activity compared with the activity of secretin alone (A) or secretin plus ascorbate (B).

	Adenylate cyclase		
	Control	Δ^9-THC	Desacetyllevonantradol
	pmol/min/mg		
A. Secretin	220	178 (81)	124 (56)
+10 μM carbachol	196 (89)	168 (76)	116 (53)
+100 μM carbachol	185 (84)	162 (74)	122 (55)
+1 μM carbachol	164 (74)	166 (75)	118 (54)
B. Secretin + ascorbate	247	177 (72)	119 (48)
+1 μM epinephrine	206 (83)	168 (68)	119 (48)
+10 μM epinephrine	102 (68)	153 (62)	132 (53)
+100 μM epinephrine	181 (73)	142 (57)	108 (44)

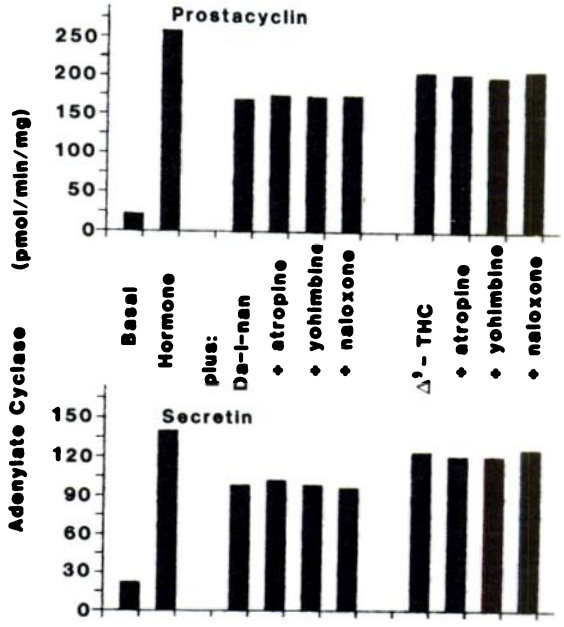

FIG. 3. *Failure of antagonists to block cannabinoid effects*

Adenylate cyclase, measured as described in the text, was stimulated by either 1.0 μM prostacyclin or 2 μM secretin. The antagonists 10 μM atropine, 50 μM naloxone, or 50 μM yohimbine were included where indicated. Either Δ^9-THC or desacetyllevonantradol (*Da-l-nan*) was present at 10 μM. This single experiment is representative of three to five performed using different concentrations of these antagonists.

neal injections of Δ^9-THC increased brain cyclic AMP at low doses and reduced it at higher doses. They correlated this biphasic response with the biphasic changes in brain catecholamine content. In further studies (12), these investigators measured a 20% increase in unstimulated adenylate cyclase activity in crude brain homogenates after intraperitoneal injection of the low dose of Δ^9-THC, and no change after the high dose. Δ^9-THC (2 to 200 μM) added to the homogenate increased norepinephrine-stimulated adenylate cyclase activity 2-fold (12). However, 2 μM cannabinol elicited a 3-fold increase in activity, suggesting that little pharmacological specificity can be associated with this *in vitro* effect. It is difficult to compare these results with the results we are reporting because of the differences in experimental technique. For example, Dolby and Kleinsmith assayed adenylate cyclase in an unpurified brain homogenate without controlling for GTP concentrations.

Kelly and Butcher (13) noted that Δ^9-THC antagonized the effects of prostaglandin E_1 and epinephrine to increase cyclic AMP accumulation in an intact cultured fibroblast system. They later demonstrated that the major effect of "low" concentrations of Δ^9-THC (5 μM) was to reduce the escape of cyclic AMP into the medium (14). Only at higher concentrations of Δ^9-THC was hormone-stimulated intracellular cyclic AMP content decreased, an effect the authors attributed to cannabinoid interference at a plasma membrane site between the hormone receptor and adenylate cyclase (14). Cannabinol and cannibidiol, compounds having little or no psychoactive properties, produced this decrement in activity more

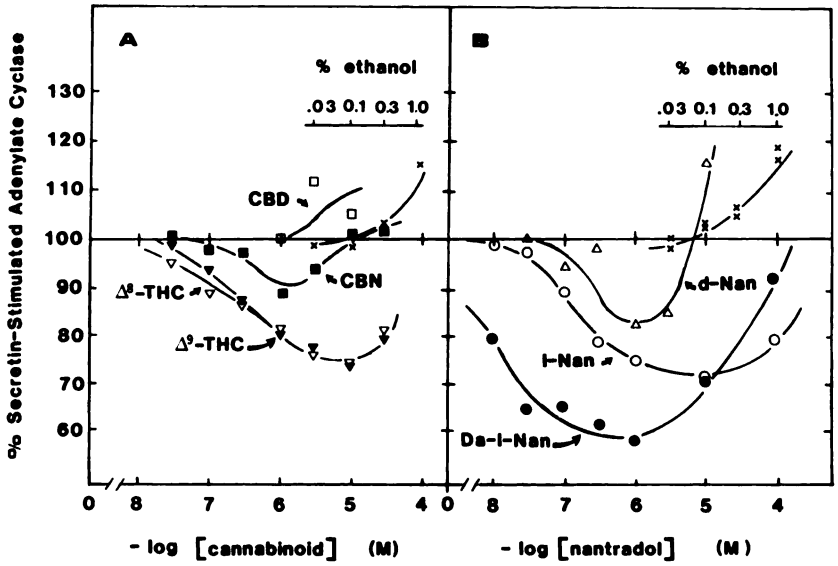

FIG. 4. *Log dose-response curve of cannabinoid drugs*

Secretin was present at 1.0 μM in all tubes. The specific activities representing 100% were 128 and 158 pmol/min/mg for the experiments in A and B, respectively. The cannabinoid compounds were serially diluted into 20 mM Na-HEPES buffer from stocks originally stored in absolute ethanol. The concentrations of ethanol present with each cannabinoid drug at 30 μM were 0.038% for Δ^9-THC (▼), 0.093% for Δ^8-THC (▽), and 0.3% for cannabinol (*CBN*, ■) and cannabidiol (*CBD*, □). Ethanol was present at 1.0% for dextronantradol (*d-Nan*, △), levonantradol (*l-Nan*, ○), and desacetyllevonantradol (*Da-l-Nan*, ●) at 100 μM. Ethanol alone (×) is plotted as the concentration corresponding to those present with cannabinol, cannabidiol, and the nantradol compounds. These experiments were repeated three (A) and four (B) times with similar results.

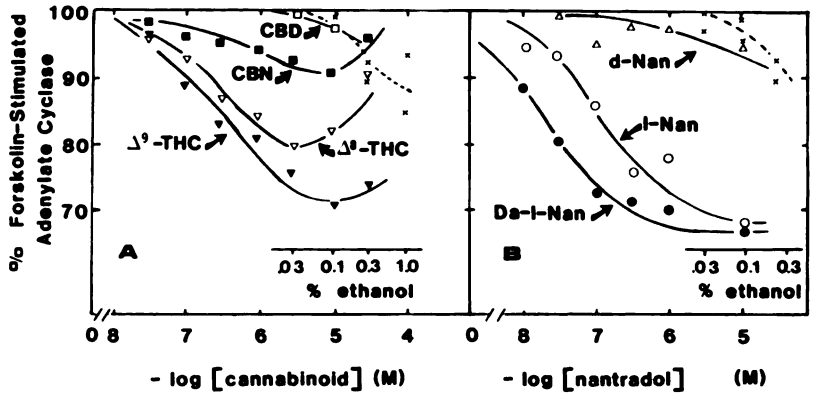

FIG. 5. *Cannabinoid inhibition of forskolin-stimulated adenylate cyclase*

See Fig. 4 for experimental design and for symbols. Forskolin was present at 1.0 μM (contributing an ethanol concentration of 0.0033%). The specific activity representing 100% was 150 pmol/min/mg. Ethanol concentrations added with the cannabinoid drugs are the same as in Fig. 4. The experiments shown were each repeated twice with identical results.

effectively than did Δ^9-THC. Cellular synthesis of cyclic AMP from labeled adenine was increased when cells were incubated with Δ^9-THC alone or in the presence of a phosphodiesterase inhibitor (14). This latter result would suggest an activation of adenylate cyclase; however, no direct measures of cannabinoid effects on membrane adenylate cyclase were made in this study. It is possible that the high cannabinoid drug and ethanol concentrations used in these studies resulted in membrane effects leading to an uncoupling of receptors from adenylate cyclase.

Most recently, Hillard and Bloom (15) observed a 25% increase in unstimulated adenylate cyclase activity in response to cannabinoid compounds in a mouse cerebral cortex homogenate. These effects were stereospecific for the nantradol compounds, but not pharmacologically selective for biologically active cannabinoid drugs. The threshold drug concentration necessary for a significant increase in adenylate cyclase activity was 10 μM. The effects were not observed if aspirin or indomethacin were present in the incubation, leading these investigators to speculate that the cyclic AMP increase was secondary to prostaglandin synthesis.

One of the most difficult experimental problems encountered in cannabinoid drug research has been distinguishing pharmacologically specific and stereoselective drug effects from the alteration of cell membrane properties by lipid interactions. The membrane/buffer partition coefficients at 4 μM Δ^9-THC were determined to be 800 and 400 in erythrocyte ghosts and synaptosomal membranes, respectively (16). In another study, the synaptosomal partition coefficient for Δ^9-THC was 12,500

over a concentration range of 10 nM to 1 μM (17). Increased fluidity of cholesterol/lecithin bilayers produced by cannabinoid compounds apparently saturates at a limit less than that produced by general anesthetics. Thus, cannabinoid drugs have been classified as "partial anesthetics" (18), and even high doses of these compounds are not able to produce surgical anesthesia in animals (17).

Certain neurochemical effects of cannabinoid drugs may be associated with lipid membrane fluidity changes. A recent preliminary report from Hillard *et al.* (19) indicates that 3 to 10 μM Δ^9-THC increased synaptic plasma membrane fluidity as determined by diphenylhexatriene fluorescence polarization. These concentrations coincide with the point of reversal of inhibition of adenylate cyclase in the present investigation. These concentrations of cannabinoid drugs were also used in the studies described above in which increased cyclic AMP production was reported (12, 14, 15).

Another factor to be considered in adenylate cyclase studies is the solvent concentration added to the reactions. In the present investigation, a critical concentration of ethanol increased hormone-stimulated adenylate cyclase activity (see Fig. 4). Stimulation of basal and hormone-stimulated adenylate cyclase activity by low ethanol concentrations has been previously reported for several systems (see ref. 20 and references contained therein). This may be due to increased fluidity of the membrane, demonstrated to occur at 0.2 to 1.7% ethanol (21). In contrast, and consistent with our findings, similar concentrations of ethanol inhibited adenylate cyclase activity in the presence of forskolin (22). The report by Dolby and Kleinsmith (12) that cannabinoid drugs increased adenylate cyclase activity in brain homogenates, was performed with 3% ethanol in all reaction tubes. It is unclear what effect this may have produced on the experimental results, but it leaves the interpretation of a cannabinoid effect subject to speculation.

The present study has provided evidence consistent with the existence of a membrane receptor for the inhibition of adenylate cyclase by cannabinoid drugs. The dose dependence of the inhibitory phase of the concentration-response curve is consistent with a drug-receptor interaction. The inhibitory activity occurs in a concentration range corresponding to that which might be expected for the neuronal environment concurrent with the *in vivo* effects. Gill and Jones (23) measured 1.5 μmol/kg Δ^9-THC in brain tissue at the peak of the behavioral response in mice. Similar values could be estimated from the data of Ohlsson *et al.* (24) for Δ^8-THC in mice, and were determined for Δ^8-THC, Δ^9-THC, and cannabinol in rats (25).

The cannabinoid drug potency series described for the adenylate cyclase inhibition corresponds to that for the cardiovascular and psychometric parameters of these compounds in man (8, 10). Stereospecificity has been demonstrated for the nantradol compounds both in the inhibition of adenylate cyclase described here, and in animal tests (2). Levonantradol and desacetyllevonantradol were 50 to 100 times more potent than Δ^9-THC in a battery of analgesic tests, but had similar potency in a behavioral measure in dogs (9). The inconsistency in these responses may suggest a divergence of effects that may represent interactions with more than one pharmacological system in the brain.

A number of neurotransmitter systems have been implicated in the mechanism of action of cannabinoid drugs. Psychoactive cannabinoid compounds have been associated with alterations in dopaminergic (26–28), noradrenergic (27–29), histaminergic (30), and serotonergic (26, 27, 29) functions. A considerable body of evidence suggests that *in vivo* actions of cannabinoid drugs involve muscarinic cholinergic systems (31, 32). Other *in vivo* pharmacological studies provide evidence for an involvement of cannabinoid drugs with opioid systems (28, 33–35).

Inhibition of adenylate cyclase by *alpha*-adrenergic and muscarinic cholinergic agonists, opiates, adenosine, prostaglandin E_2, somatostatin, dopamine, and insulin has been demonstrated in a variety of cell types (see ref. 36 for review and references). It is possible that the cannabimimetic drugs may be acting via one of these receptors or at some as yet unidentified neuronal receptor.

We would like to propose the testable hypothesis that the inhibition of adenylate cyclase by cannabimimetic drugs is a pharmacologically specific, receptor-mediated event, and that the reversal of this effect observed at higher drug concentrations is associated with membrane perturbations. Studies are currently being performed in this laboratory that are designed to test this hypothesis.

ACKNOWLEDGMENT

The secretarial assistance of Maggie Klevorn is appreciated.

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