3273

Brain Research, 162 (1979) 77–88
© Elsevier/North-Holland Biomedical Press

INTERACTION OF LSD AND OTHER HALLUCINOGENS WITH DOPAMINE-SENSITIVE ADENYLATE CYCLASE IN PRIMATE BRAIN: REGIONAL DIFFERENCES

HO SAM AHN and MAYNARD H. MAKMAN

Departments of Biochemistry and Molecular Pharmacology, Albert Einstein College of Medicine, Bronx, N.Y. 10461 (U.S.A.)

(Accepted May 18th, 1978)

SUMMARY

The influence of D-lysergic acid diethylamide (LSD) and mescaline on adenylate cyclase activity was studied in homogenates of Cebus and rhesus monkey anterior limbic cortex (ALC), frontal cortex (FC), caudate nucleus and retina. Previous studies have shown these tissues to contain dopamine-stimulated adenylate cyclase (AC). In addition, we are now reporting the presence of a dopamine-sensitive adenylate cyclase in the auditory cortex. AC of ALC and auditory cortex was stimulated by LSD and mescaline, whereas activity of FC, caudate nucleus and retina was not stimulated by the same agents. In contrast to regional specificity for stimulation, LSD was capable of antagonizing dopamine-stimulated activity in all brain regions examined.

LSD and mescaline produced similar maximal stimulation (about 70%) of AC of ALC homogenates, but the EC_{50} for LSD (0.43 μM) was about one-tenth that for mescaline (4.5 μM). Similar relative potencies were also observed for the auditory cortex enzyme. Although much weaker than LSD, methamphetamine also produced a dose-dependent stimulation of ALC AC. Both agonist and antagonist effects of the hallucinogens appear to involve interaction with dopamine receptors; LSD- or methamphetamine-stimulated activity in ALC was blocked by haloperidol and fluphenazine, which are dopamine antagonists, but not by phentolamine, an α-receptor blocker. Antagonism of dopamine by LSD in both ALC and FC was found to be competitive and mescaline was an effective but weaker antagonist than was LSD. In addition, neither histamine — nor Gpp(NH)p — stimulated activity of FC was inhibited by LSD. It is proposed that the occurrence of dopamine agonistic action of hallucinogens in only certain regions of primate brain may provide a basis for at least some of the behavioral effects of LSD, mescaline and methamphetamine in primates.

INTRODUCTION

The mechanisms involved in the psychotomimetic actions of various hallucinogenic agents including D-lysergic acid diethylamide (LSD) are poorly understood[2,10,22,37]. Biochemical[6,14,16], physiological[1,36] and behavioral[15,19,20,32] studies suggest that LSD and related hallucinogens may interact with central monoaminergic receptors. Considerable evidence suggests that dopamine functions as a neurotransmitter in the central nervous system and the synaptic actions of this amine may be mediated at least in part by cyclic AMP (cAMP) formed at postsynaptic receptor sites[17]. Since pharmacologic evidence implicated brain dopamine receptors in psychotic disorders as well as experimental psychoses (e.g., amphetamine-induced psychosis)[33], it is possible that psychotomimetic effects of LSD and other hallucinogens may be mediated at least partially by their interaction with dopaminergic receptor systems. A number of behavioral and neurochemical studies in animals have indicated that LSD interacts with dopamine receptors in vivo[14,16,20,27,30-32]. In recent studies mainly using rat brain cell-free preparations, LSD was found to interact with dopamine-sensitive adenylate cyclase in certain brain regions. LSD stimulated the activity of dopamine-sensitive adenylate cyclase in cell-free preparations of caudate, retina, nucleus accumbens and limbic cortex of rat brain and retina of rat, rabbit, calf and cat[14,34,35,40,42]. LSD also blocked the dopamine stimulation of the cyclases in certain brain regions[9,14,34,40,42] and retina[25]. These results are in agreement with recent receptor binding studies suggesting that LSD acts as a mixed dopamine agonist-antagonist at dopamine receptors[12,13].

Recent work from our laboratory indicates that pharmacologic properties of dopamine receptor-adenylate cyclases differ in the various regions of monkey brain receiving dopaminergic innervations[3,5,24,29]. These results, together with the ability of LSD to interact with central dopamine receptors described above, point to a possibility that the effect of LSD on dopamine-sensitive adenylate cyclase may vary in different regions of primate brain. To evaluate this possibility, we examined in this study the effect of LSD on basal and dopamine-stimulated adenylate cyclase activity in various regions of monkey brain. Also included in this study were mescaline and methamphetamine. We now report that, in addition to LSD, mescaline and methamphetamine are capable of stimulating adenylate cyclase activity, and that there are regional differences in response to LSD and mescaline in primate brain.

MATERIALS AND METHODS

Twelve monkeys (10 *Cebus apella* and 2 *Macaca mulatta*) ranging in age between 3 and 5 years were used. Brain tissues were dissected out from frontal orbital regions (frontal cortex), anterior portion of areas 24 and 25 of Walker and Broadman[43] (anterior limbic cortex), area A1[45] (primary auditory cortex), caudate nucleus and retina of Nembutal (50-70 mg/kg, i.p.) anesthetized animals. Excised tissue was washed with isotonic NaCl solution and gently homogenized by hand in a loose-fitting all-glass Kontes homogenizer at 0-4°C in 2 m*M* Tris-maleate buffer containing 0.8 m*M*

EGTA at dilutions of 1:40 (wet wt./vol.) for frontal cortex and auditory cortex, or 1:60 for anterior limbic cortex, retina and caudate nucleus. Since the response to hallucinogens of sensitive tissues markedly declined upon freezing and storage of brain tissue, adenylate cyclase assays were carried out using homogenates of fresh brain tissue.

Basal and agent-stimulated adenylate cyclase activities were measured as described[5] with a minor modification. The reaction mixture in a total volume of 100 μl contained 80 m*M* Tris·maleate buffer (pH 7.4), 5 m*M* theophylline, 2 m*M* $MgSO_4$, 0.5 m*M* ATP, 25 μl of brain homogenate and appropriate hallucinogens or other agents. The reaction was initiated by addition of the homogenate and was allowed to proceed for 5 min at 30 °C in a shaking water bath. The reaction was terminated by placing the assay tubes in a boiling water bath for 3 min. Particulate matter was removed by low-speed centrifugation and aliquots of the supernatant fluids were assayed for cAMP by a protein-binding assay previously described[11]. All values were corrected for the small amount of endogenous cAMP present in control samples which were incubated at 30 °C without substrate. Each experiment involved triplicate adenylate cyclase incubations for every condition studied, together with replicate determinations of cAMP. Protein was measured by the method of Lowry et al.[23]. A Student's *t*-test was used to determine the significance of stimulation by hallucinogens and other agents.

RESULTS

Stimulatory effects of LSD and mescaline on adenylate cyclase activity in various brain regions of Cebus monkey

LSD was found in the present study to stimulate adenylate cyclase activity in homogenates of anterior limbic cortex and auditory cortex, but not of frontal cortex, caudate nucleus or retina, of Cebus monkey (Table I), indicating regional difference in responsiveness to LSD. Mescaline, another hallucinogen exhibiting cross-tolerance with LSD, also stimulated adenylate cyclase activity of anterior limbic cortex and auditory cortex, but not of frontal cortex and caudate nucleus, in parallel with the

TABLE I

Regional differences in responsiveness of monkey CNS adenylate cyclase to LSD and mescaline

Homogenates of Cebus monkey brain regions and retina were prepared and assayed as described in Materials and Methods. Values are expressed in pmole cAMP formed/mg protein/5 min. Per cent stimulations due to agents are in parentheses. Each agent added is at a final concentration of 10 μ*M* for all regions except for retina (6 μ*M* LSD). Each value represents a mean ± S.E.M. for 4 (auditory cortex, caudate nucleus) or 12 (anterior limbic and frontal cortex) separate incubations (1 or 3 separate experiments) each assayed in duplicate.

Agents added	*Anterior limbic cortex*	*Frontal cortex*	*Auditory cortex*	*Caudate nucleus*	*Retina*
None	106 ± 10	182 ± 11	83 ± 9	394 ± 5	124 ± 13
LSD	180 ± 7 (+70)	171 ± 15 (—6)	151 ± 11 (+82)	301 ± 13 (—24)	140 ± 14 (+13)
Mescaline	162 ± 15 (+38)	166 ± 6 (—9)	116 ± 8 (+40)	376 ± 32 (—5)	

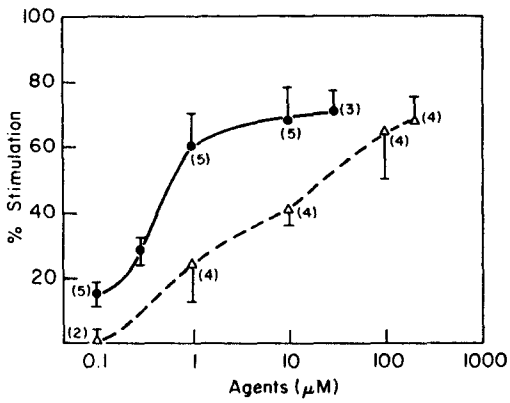

Fig. 1. Dose-dependent stimulation of adenylate cyclase activity by LSD and mescaline in Cebus monkey anterior limbic cortex homogenates. Basal activity was 123 ± 8 pmole cAMP/mg protein/5 min (mean ± S.E.M. for 5 separate experiments). Each point and vertical bar represents the mean ± S.E.M. of 6–15 incubations. Numbers of experiments are in parentheses. ●——●, LSD, △----△, mescaline.

effect of LSD (Table I). Effects of varying concentrations of LSD and mescaline on the adenylate cyclase activity were then examined in the anterior limbic cortex of Cebus monkey. The enzyme activity was increased by 70% in the presence of LSD at maximally effective concentrations (Fig. 1). A significant stimulation (15%, $P < 0.05$) was observed at a concentration as low as 10^{-7} *M* and the EC_{50} (concentration for half-maximal stimulation) for LSD was 4.3×10^{-7} *M*, which is comparable to the reported values (1.4×10^{-7} *M* and 5×10^{-7} *M*) for rat striatum[9,42]. Although LSD and mescaline, at maximally effective concentrations (10^{-5} *M* for LSD and 10^{-4} *M* for mescaline), produced about the same magnitude of stimulation, LSD was more effective than mescaline at submaximal concentrations (EC_{50} for mescaline 4.5×10^{-6} *M*) (Fig. 1). Similar relative potencies of LSD and mescaline were also found for the auditory cortex adenylate cyclase (results not shown).

Effect of α- and dopamine-receptor antagonists on LSD-stimulated adenylate cyclase activity

In an attempt to characterize pharmacologically the receptor mediating the stimulation by LSD of adenylate cyclase, the effects of receptor blocking agents were examined. The LSD (1 μ*M*)-stimulated activity in the anterior limbic cortex was antagonized more than 50% by the dopamine receptor antagonists fluphenazine and haloperidol at 0.1 μ*M*, but was not significantly blocked ($P < 0.1$) by 0.1 μ*M* phentolamine, an α-adrenergic receptor blocker (Table II). These blocking agents at the concentration used did not affect the basal enzyme activity (results not shown). It should be noted that the approximately equal potencies of haloperidol and fluphenazine in blocking LSD stimulation of cyclase activity paralleled their antagonistic potencies[24,29] on the dopamine-stimulated activity in the anterior limbic cortex, thus further suggesting the interaction of LSD with dopamine receptor adenylate cyclase.

TABLE II

Influence of blocking agents and LSD-stimulated adenylate cyclase activity of Cebus monkey anterior limbic cortex

Each value is a mean ± S.E.M. for two separate experiments. n.s. = not statistically significant ($P > 0.05$). Final concentrations are 1 μM LSD and 0.1 μM antagonist. Values in parenthesis indicate significance (P values) of difference between LSD and LSD plus blocking agent. Different monkeys were used for separate experiments.

Agents added	*pmole cAMP formed/ mg protein/5 min*	*Inhibition due to antagonist (%)*
none	142 ± 5	
LSD	267 ± 10	
LSD + phentolamine	236 ± 16 (n.s.)	25
LSD + haloperidol	183 ± 20 ($P < 0.01$)	67
LSD + fluphenazine	186 ± 10 ($P < 0.001$)	65

Antagonist effects of LSD on dopamine-stimulated adenylate cyclase activity in different brain regions

Since the above studies with blocking agents indicate a possible interaction of LSD with dopamine receptors, the effect of LSD on dopamine-stimulated adenylate cyclase activity was investigated in anterior limbic cortex, auditory cortex, frontal cortex, caudate nucleus and retina of Cebus monkeys. Dopamine produced from 100 to 300% stimulation of enzyme activity in these regions of monkey brain, with greatest stimulation found in the auditory cortex (Table III). The dopamine-stimulated activities in these brain regions were all significantly blocked by LSD at concentrations 1/2 to 1/50 those of dopamine (Table III) in contrast to the stimulatory effect of LSD, which was observed only in anterior limbic cortex and auditory cortex. These results, together with the aforementioned stimulatory effect of LSD, indicate that LSD can act as a mixed agonist and antagonist for dopamine sensitive adenylate cyclase in anterior limbic cortex and auditory cortex. This is in line with earlier studies[14,31,35,40] of adenylate cyclase activity of various rat brain regions, as well as with studies of dopamine receptor radioligand binding of calf caudate nucleus[12,13]. Mescaline at 100 μM also caused 51 ± 14% inhibition ($P < 0.02$ for 2 separate experiments) of the dopamine (50 μM)-stimulated cyclase activity in Cebus monkey frontal cortex.

In order to further examine whether LSD and dopamine directly interact with the same receptor sites, the dose–response curves for cyclase activation were compared in the presence of either dopamine alone or dopamine plus a fixed concentration of LSD (10 μM or 1 μM) in anterior limbic cortex and frontal cortex of Cebus monkeys. LSD lowered the apparent affinity of dopamine receptor for dopamine in both regions: the affinity decreased from 0.5 to 10 μM by 1 μM LSD and even further by 10 μM LSD in anterior limbic cortex, and from 1 to 50 μM by 10 μM LSD in frontal cortex (Fig. 2A and B). In addition, the same maximal stimulation of activity was observed in the presence or absence of LSD in anterior limbic cortex, indicating competitive interaction between LSD and dopamine for the same receptor. Although a submaximal stimulation of activity was obtained by 100 μM dopamine in the presence

TABLE III

Inhibitory effect of LSD on dopamine-stimulated adenylate cyclase activity in various regions of Cebus monkey cerebral cortex

Dopamine-stimulated adenylate cyclase activities in Cebus monkey frontal cortex (100 μM DA) and anterior limbic cortex (50 μM DA) were inhibited by 10 μM fluphenazine 85% and 90%, respectively. $P < 0.01$ for the difference between the value obtained with dopamine and the value obtained with dopamine plus LSD in all regions except for caudate nucleus ($P < 0.05$).

Brain regions and agents added	*pmole cAMP formed/ mg protein/5 min*	*Per cent stimulation*
*Frontal cortex**		
None	160 ± 20	
Dopamine, 100 μM	344 ± 26	115
LSD, 10 μM	147 ± 12	—8
Dopamine, 100 μM + LSD, 10 μM	246 ± 18	54 (—46)
*Anterior limbic cortex**		
None	126 ± 3	
Dopamine, 50 μM	307 ± 16	144
LSD, 10 μM	193 ± 16	53
Dopamine, 50 μM + LSD, 10 μM	215 ± 10	71 (—88)
*Auditory cortex***		
None	83 ± 9	
Dopamine, 100 μM	330 ± 9	298
LSD, 10 μM	151 ± 11	82
Dopamine, 100 μM + LSD, 10 μM	290 ± 7	249 (—44)
*Caudate nucleus***		
None	394 ± 5	
Dopamine, 50 μM	830 ± 25	111
LSD, 1 μM	410 ± 17	4
Dopamine, 50 μM + LSD, 1 μM	680 ± 38	73 (—36)
*Retina**		
None	124 ± 13	
Dopamine, 10 μM	337 ± 30	172
LSD, 6 μM	140 ± 14	13
Dopamine, 10 μM + LSD, 6 μM	192 ± 4	55 (—76)

* Each value is an average of two separate experiments ± S.E.M.

** Each value is an average of 3 incubations ± S.E.M. in one experiment. The numbers in parentheses (Δ) represent per cent inhibition due to LSD: these values were calculated from the following equation

$$\text{per cent inhibition} = \left[\frac{\text{(Activity with DA plus LSD)-(Activity with LSD)}}{\text{(DA-activated activity)-(Basal activity)}} - 1\right] \times 100$$

of 10 μM LSD in frontal cortex (Fig. 2B), the same maximal stimulation (with 100 μM dopamine) was observed in the presence or absence of 5 μM LSD (data not shown).

Comparison of effects of LSD on histamine, dopamine and Gpp(NH)p-stimulated activity

In order to ascertain specificity of the inhibitory action of LSD on the dopamine receptor, effects of LSD on histamine- and Gpp(NH)p-stimulated cyclase activity were also investigated in rhesus monkey frontal cortex. Dopamine, histamine and Gpp-(NH)p-stimulated cyclase activity 80%, 103% and 779%, respectively (Table IV).

Although LSD (2 μM) inhibited the dopamine-stimulated activity by 46 %, it failed to antagonize the histamine- or Gpp(NH)p-induced stimulation of cyclase activity, thus indicating a specific inhibition of the dopamine receptor by LSD (Table IV).

Interaction of methamphetamine with adenylate cyclase

Since adenylate cyclase of anterior limbic cortex was stimulated by LSD and

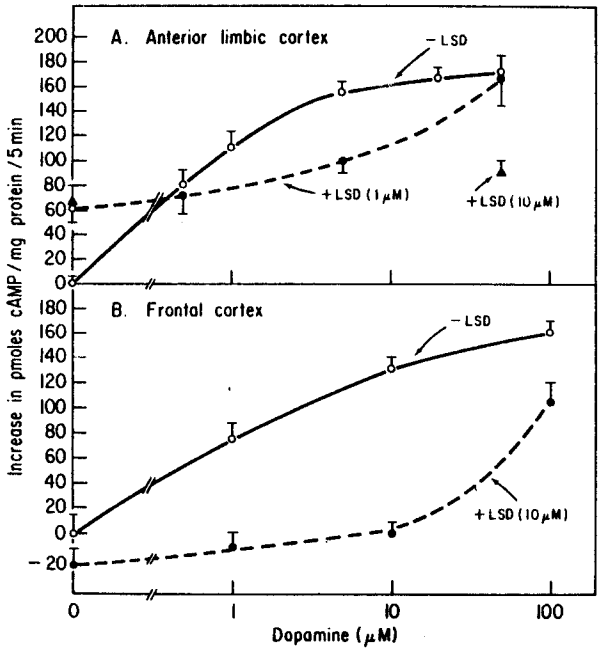

Fig. 2. Effect of various concentrations of dopamine on the activity of adenylate cyclase in frontal cortex (FC) and anterior limbic cortex (ALC) of Cebus monkey in the presence and absence of LSD. Basal enzyme activities in the absence of added agents were 170 ± 14 and 122 ± 6 pmole cAMP/mg protein/5 min (mean ± S.E.M. for 6 determinations), respectively, for FC and ALC. A: anterior limbic cortex; B: frontal cortex. ○——○, without LSD; ●----●, with LSD. The final concentrations of LSD were 10 μM for frontal cortex and 1 or 10 μM for anterior limbic cortex.

TABLE IV

Influence of LSD on dopamine-, histamine- and Gpp(NH)p-stimulated adenylate cyclase activities in rhesus monkey frontal cortex

Final concentrations are 30 μM for all agents except for LSD (2 μM). Each value represents mean ± S.E.M. for 3 incubations. Each assay in duplicate. Values in parenthesis indicate significance of differences between values of agent alone and LSD plus agent. n.s. = not significant at $P < 0.05$.

Agents added	*pmole cAMP formed/ mg protein/5 min*	*Change due to LSD (%)*
None	170 ± 12	
LSD	170 ± 7	
Dopamine	306 ± 16	
Histamine	345 ± 14	
Gpp(NH)p	1494 ± 21	
Dopamine + LSD	243 ± 15 ($P < 0.05$)	—46
Histamine + LSD	354 ± 23 (n.s.)	+ 5
Gpp(NH)p + LSD	1450 ± 41 (n.s.)	—3

TABLE V

Effect of methamphetamine and ephedrine on adenylate cyclase activity in homogenate of rhesus monkey anterior limbic cortex

Each value represents mean ± S.E.M. for 1–3 experiments. n.s. = not significant. *P* values for significance of stimulation are in parentheses.

Agents added	*pmole cAMP formed/ mg protein/5 min*	*Stimulation (%)*
None	78 ± 7***	
Methamphetamine, 1 μM	101 ± 10* (n.s.)	29
Methamphetamine, 10 μM	119 ± 10*** ($P < 0.1$)	53
Methamphetamine, 100 μM	128 ± 8*** ($P < 0.001$)	64
Ephedrine, 100 μM	98 ± 5** ($P < 0.05$)	26

* An average of 1 experiment.
** An average of 2 experiments.
*** An average of 3 experiments.

mescaline, hallucinogens with cross-tolerance, the influence of another type of hallucinogen, methamphetamine, was examined on adenylate cyclase activity of rhesus monkey anterior limbic cortex. Methamphetamine, an amphetamine analog, stimulated activity of the anterior limbic cortex in a dose-dependent manner at concentrations ranging from 1 μM to 100 μM, with an EC_{50} a little higher than 1 μM (Table V). Ephedrine, a structural analog of methamphetamine, at 100 μM also caused a small but significant stimulation of activity (Table V). Additional studies with blocking agents revealed that the methamphetamine (50 μM)-stimulated activity was more effectively blocked by haloperidol than by phentolamine or propranolol at a concentration 1/10 that of methamphetamine (data not shown).

DISCUSSION

Earlier investigations from this laboratory demonstrated the presence of dopamine-sensitive adenylate cyclases in frontal cortex, retina, caudate nucleus and anterior limbic cortex of Cebus and rhesus monkey brain[5,25,28], and further indicated regional differences in pharmacologic properties of dopamine receptors in these regions on the basis of their relative responsiveness to dopamine agonists and antagonists[5,24,29]. The present study reveals for the first time the occurrence of dopamine-sensitive adenylate cyclase in primary auditory cortex. This activity exhibits a greater maximal response to dopamine than any other region of Cebus monkey brain examined. The presence of this activity, together with the known dopaminergic innervation[8,21] in auditory cortex, suggests a functional role of dopamine-stimulated adenylate cyclase in auditory transmission.

Results in this study demonstrate a differential response of various regions of Cebus monkey brain to the stimulatory effects of LSD and mescaline. Thus, adenylate cyclase activity of anterior limbic cortex and auditory cortex, but not of frontal cortex, caudate nucleus and retina, was stimulated by LSD and mescaline. Stimulation of

adenylate cyclase activity by LSD was previously reported for caudate and mesolimbic areas of rat brain and retina of non-primate species[34,10]. Selective stimulation by LSD and possibly mescaline of dopamine sensitive adenylate cyclase activity in certain monkey brain regions is in contrast to its reported stimulation of the activity in most of rat brain areas examined[35], indicating a possible species difference. Also, the magnitude of stimulation by LSD observed in the present study is greater than that reported in previous studies of non-primate brain (see Introduction for references). A dose-dependent stimulation of adenylate cyclase in anterior limbic cortex and auditory cortex of Cebus monkey in this study is the first observation of direct stimulation of adenylate cyclase by mescaline in cell-free preparations, and contrasts with the reported lack of its stimulatory effect on cyclase activity in rat superior colliculi and striatal preparations[41,42]. In slice preparations of rat brain stem, mescaline and other hallucinogens (e.g. psilocybin, LSD, *N*,*N*-dimethyltryptamine) were earlier reported to elicit a two-fold increase in cAMP[38].

In contrast to the stimulatory effect of LSD and mescaline in only selective regions, the inhibitory effect of LSD on dopamine-stimulated activity was observed in all brain regions examined. Although considerably weaker than LSD, mescaline at high concentrations also had a significant inhibitory effect on dopamine-stimulated activity. Inhibition of dopamine-stimulated activity as well as stimulation of basal activity by LSD were also previously reported for rat striatum[9,14,35,10,42]. Since neither histamine-stimulated activity nor Gpp(NH)p-stimulated activity in monkey frontal cortex was inhibited by LSD, this inhibitory effect appeared to involve a specific antagonism of dopamine. These findings together with the data for competitive antagonism by LSD of dopamine-stimulated activity in monkey brain regions and for inhibition of LSD-stimulated activity in limbic cortex by dopamine antagonists suggest a direct interaction of LSD with dopamine receptors to effect stimulation or inhibition of dopamine-sensitive adenylate cyclases. In support of this interpretation are recent findings[12,13] that LSD had very high affinity for dopamine binding sites in non-primate brain, and that it also acted as a mixed dopamine agonist-antagonist based on its similar affinities for tritiated dopamine agonist and antagonist binding sites. The ability of LSD to block dopamine receptors in all primate brain regions examined but to stimulate dopamine-sensitive activity only in selective regions suggests that molecular interactions between LSD and dopamine receptors may be required for activation of cyclase activity in addition to those required for binding and competitive inhibition of dopamine-stimulated activity. Methamphetamine, probably representative of a class of psychotomimetic drugs different from that of LSD and mescaline[2,44], also stimulated adenylate cyclase activity of anterior limbic cortex, and the stimulatory effect of methamphetamine was effectively antagonized by haloperidol. This finding indicates a direct receptor stimulation by the drug which would be in addition to the well-known presynaptic actions of amphetamine and its derivatives on catecholamine release and uptake.

It seems possible that the activation of dopamine-sensitive adenylate cyclase in monkey anterior limbic cortex and auditory cortex by these hallucinogens may be responsible for at least some component of their psychotropic effects. Consistent with

this possibility is the finding that the minimal effective concentrations of these hallucinogens (0.1 μM for LSD, about 1 μM for mescaline and between 1 and 10 μM for methamphetamine) in stimulating anterior limbic cortex adenylate cyclase are comparable and parallel to the reported values[39] of their minimal effective brain levels in an animal behavior test (0.5 nmole/g for LSD, 5 nmole/g for mescaline and 25 nmole/g for amphetamine). However, the relative potencies of LSD and mescaline for psychedelic effects in man[18] differ much more markedly from one another than is the case for the animal studies[39] or adenylate cyclase studies reported here. Also, the psychedelic effects of methylamphetamine differ qualitatively from those of LSD[22,26]. These findings taken together suggest that the stimulatory effects of hallucinogens on anterior limbic cortex adenylate cyclase may be responsible for abnormal behavior in animals, but may not be directly related to their psychedelic action(s).

LSD has been found to have high affinity for central serotonin binding sites[7] as well as for dopamine binding sites[12,13], as described previously. We have recently found that monkey anterior limbic cortex contains not only a dopamine- but also serotonin-sensitive adenylate cyclase that is also sensitive to neuroleptic drugs[4], and the characteristics of this serotonin system, including possible interactions of hallucinogens, will be described in a separate communication. The data reported in the present study, in conjunction with our previous reports[3,5,24,29], indicate that regional differences in dopamine receptor-adenylate cyclase systems include differences in response to hallucinogens. Further studies will be required to assess the functional significance of these findings.

ACKNOWLEDGEMENTS

This work was supported by Grants NS 09649 and IF22 MH 01955-03 from the U.S. Public Health Service.

We wish to thank Dr. R. Katzman and Dr. E. Gardner for their advice during the course of these studies and for their assistance in dissection of monkey brain tissues.

REFERENCES

1 Aghajanian, G. K., Influence of drugs on the firing of serotonin-containing neurons in brain, *Fed. Proc.*, 31 (1972) 91–96.
2 Aghajanian, G. K., Haigler, H. J. and Bennett, J. L., Amine receptors in CNS. III. 5-Hydroxytryptamine in brain. In L. L. Iversen, S. D. Iversen and H. Snyder (Eds.), *Handbook of Psychopharmacology, Vol. 6*, Plenum Press, New York, 1975, pp. 63–95.
3 Ahn, H. S. and Makman, M. H., Neurotransmitter-sensitive adenylate cyclase in the hypothalami of guinea pig, rat and monkey, *Brain Research*, 138 (1977) 125–138.
4 Ahn, H. S. and Makman, M. H., Serotonin sensitive adenylate cyclase activity in monkey anterior limbic cortex: antagonism by molindone and other antipsychotic drugs, *Life Sci.*, 23 (1978) 507–512.
5 Ahn, H. S., Mishra, R. K., Demirjian, C. and Makman, M. H., Catecholamine-sensitive adenylate cyclase in frontal cortex of primate brain, *Brain Research*, 116 (1976) 437–454.
6 Andén, N.-E., Corrodi, H., Fuxe, K. and Hökfelt, T., Evidence for a central 5-hydroxytryptamine receptor stimulation by lysergic acid diethylamide, *Brit. J. Pharmacol.*, 34 (1968) 1–7.
7 Bennett, J. P., Jr. and Snyder, S. H., Serotonin and lysergic acid diethylamide binding in rat brain

membranes: relationship to postsynaptic serotonin receptors, *Molec. Pharmacol.*, 12 (1976) 373–389.

8 Berger, B., Tassin, J. P., Blanc, G., Moyne, M. A. and Thierry, A. M., Histochemical confirmation for dopaminergic innervation of the rat cerebral cortex after destruction of the noradrenergic ascending pathways, *Brain Research*, 81 (1974) 332–337.

9 Bockaert, J., Prémont, J., Glowinski, J., Thierry, A. M., and Tassin, J. P., Topographical distribution of dopaminergic innervation and of dopaminergic receptors in the rat striatum. II. Distribution and characteristics of dopamine adenylate cyclase-interactions of D-LSD with dopaminergic receptors, *Brain Research*, 107 (1976) 303–315.

10 Brawley, P. and Duffield, J. C., The pharmacology of hallucinogens, *Pharmacol. Rev.*, 24 (1972) 31–66.

11 Brown, J. H. and Makman, M. H., Influence of neuroleptic drugs and apomorphine on dopamine sensitive adenylate cyclase of retina, *J. Neurochem.*, 21 (1973) 477–479.

12 Burt, D. R., Creese, I. and Snyder, S. H., Binding interactions of lysergic acid diethylamide and related agents with dopamine receptors in the brain, *Molec. Pharmacol.*, 12 (1976) 631–638.

13 Creese, I., Burt, D. R. and Snyder, S. H., The dopamine receptor: differential binding of D-LSD and related agents to agonist and antagonist states, *Life Sci.*, 17 (1976) 1715–1720.

14 DaPrada, M., Saner, A., Burkard, W. P., Bartholini, G. and Pletscher, A., Lysergic acid diethylamide: evidence for stimulation of cerebral dopamine receptors, *Brain Research*, 94 (1975) 67–73.

15 Dixon, A. K., Evidence for catecholamine mediation in the 'aberrant' behavior induced by lysergic acid diethylamide, *Experientia (Basel)*, 24 (1968) 743–747.

16 Fuxe, A., Agnati, L. F., Corrodi, H., Everitt, B. J., Hökfelt, T., Löfström, A. and Ungerstedt, U., Action of dopamine receptor agonists in forebrain and hypothalamus: rotational behavior, ovulation and dopamine turnover. In D. B. Calne, T. N. Chase and A. Barbeau (Eds.), *Advances in Neurology, Vol. 9*, Raven Press, New York, 1975, pp. 223–242.

17 Greengard, P., McAfee, D. A. and Kebabian, J. W., On the mechanism of action of cyclic AMP and its role in synaptic transmission. In P. Greengard, R., Paoletti and G. A. Robison (Eds.), *Advances in Cyclic Nucleotide Research, Vol. 1*, Raven Press, New York, 1972, pp. 337–355.

18 Hollister, L. E., Clinical pharmacology of hallucinogens and marihuana. In C. J. D. Zarafonetis (Eds.), *Drug Abuse: Proceedings of the International Conference*, Lea and Febiger, Philadelphia, 1972, pp. 321–332.

19 Johnson, A. M., Vigouret, J. M. and Loew, D. M., Central dopaminergic actions of ergotoxine alkaloids and some derivatives, *Experientia (Basel)*, 29 (1973) 763.

20 Kelly, P. H. and Iversen, L. I., LSD as an agonist at mesolimbic dopamine receptors, *Psychopharmacologia (Berl.)*, 45 (1975) 221–224.

21 Lindvall, O., Björklund, A., Moore, R. Y. and Stenevi, U., Mesencephalic dopamine neurons projecting to neocortex, *Brain Research*, 81 (1974) 325–331.

22 Logan, W. J., Neurological aspects of hallucinogenic drugs. In W. J. Friedlander (Eds.), *Advances in Neurology, Vol. 13*, Raven Press, New York, 1975, pp. 47–78.

23 Lowry, O. H., Rosebrough, N. J., Farr, A. L. and Randall, R., Protein measurement with the Folin phenol reagent, *J. biol. Chem.*, 193 (1951) 265–275.

24 Makman, M. H., Actions of cyclic AMP and relationship to transmitter function in nervous tissue. In G. Litwack (Ed.), *Biochemical Actions of Hormones, Vol. 4*, Academic Press, New York, 1977, pp. 407–496.

25 Makman, M. H., Brown, J. H. and Mishra, R. K., Cyclic AMP in retina and caudate nucleus. Influence of dopamine and other agents. In G. I. Drummond, P. Greengard and G. A. Robison (Eds.), *Advances in Cyclic Nucleotide Research, Vol. 5*, Raven Press, New York, 1975, pp. 661–679.

26 Martin, W. R., Sloan, J. W., Sapira, J. D. and Jasinski, D. R., Physiologic, subjective, and behavioral effects of amphetamine, methamphetamine, ephedrine, phenmetrazine, and methylphenidate in man, *Clin. Pharmacol. Therapeut.*, 12 (1971) 245–258.

27 Menon, M. K., Clark, W. G. and Masuoka, D. T., Possible involvement of the central dopaminergic system in the antireserpine effect of LSD, *Psychopharmacology*, 52 (1977) 291–297.

28 Mishra, R. K., Demirjian, C., Katzman, R. and Makman, M. H., A dopamine-sensitive adenylate cyclase in anterior limbic cortex and mesolimbic region of primate brain, *Brain Research*, 96 (1975) 395–399.

29 Mishra, R. K., Makman, M. H., Ahn, H. S., Dvorkin, B., Horowitz, S. G., Keehn, E. and Demirjian, C., Differences in primate brain regions in relative potency for antagonism of

dopamine-stimulated adenylate cyclases by neuroleptic drugs and possible implications for localization of antipsychotic activity, *Neurosci, Abstr.*, 2 (1976) 1134.
30 Persson, S.-A., The effect of LSD and 2-bromo-LSD on the striatal DOPA accumulation after decarboxylase inhibition in rats, *Europ. J. Pharmacol.*, 43 (1977) 73–83.
31 Persson, S.-A., Effects of LSD and 2-bromo-LSD on striatal DOPAC levels, *Life Sci.*, 20 (1977) 1199–1206.
32 Pieri, L., Pieri, M. and Haefely, W., LSD as an agonist of dopamine receptors in the striatum, *Nature (Lond.)*, 252 (1974) 586–588.
33 Snyder, S. H., Banerjee, S. P., Yamamura, H. I. and Greenberg, D., Drugs, neurotransmitters and schizophrenia, *Science*, 184 (1974) 1243–1253.
34 Spano, P. F., Kumakura, K. and Trabucchi, M., Dopamine-sensitive adenylate cyclase in the retina: a point of action for D-LSD. In E. Costa, E. Giacobini and R. Paoletti (Eds.), *Advances in Biochemical Psychopharmacology, Vol. 15*, Raven Press, New York, 1976, pp. 357–365.
35 Spano, P. F., Kumakura, K., Tonon, G. C., Govoni, S. and Trabucchi, M., LSD and dopamine-sensitive adenylate cyclase in various rat brain areas, *Brain Research*, 93 (1975) 164–167.
36 Stone, T. W., Further evidence for a dopamine receptor stimulating action of an ergot alkaloid, *Brain Research*, 72 (1974) 177–180.
37 Szara, S. I., Hallucinogens. In A. Lajtha (Ed.), *Handbook of Neurochemistry, Vol. 6*, Plenum Press, New York, 1971, pp. 441–455.
38 Uzunov, P. and Weiss, B., Psychopharmacological agents and the cyclic AMP system of rat brain. In P. Greengard, R. Paoletti and G. A. Robison (Eds.), *Advances in Cyclic Nucleotide Research, Vol. 1*, Raven Press, New York, 1972, pp. 435–453.
39 Vogel, W. H., and Evans, B. D., Structure-activity relationships of certain hallucinogenic substances based on brain levels, *Life Sci.*, 20 (1977) 1629–1636.
40 von Hungen, K., Roberts, S. and Hill, D., LSD as an agonist and antagonist of central dopamine receptors, *Nature (Lond.)*, 252 (1974) 588–589.
41 von Hungen, K., Roberts, S. and Hill, D. F., Serotonin-sensitive adenylate cyclase in immature rat brain, *Brain Research*, 84 (1975) 257–267.
42 von Hungen, K., Roberts, S. and Hill, D. F., Interactions between lysergic acid diethylamide and dopamine-sensitive adenylate cyclase systems in rat brain, *Brain Research*, 94 (1975) 57–66.
43 Walker, A. E., A cytoarchitectural study of the prefrontal area of the macaque monkey, *J. comp. Neurol.*, 72 (1940) 59–86.
44 Wolbach, A. B., Isbell, H. and Miner, E. J., Cross-tolerance between mescaline and LSD-25 with a comparison of the mescaline and LSD reactions, *Psychopharmacologia*, 3 (1962) 1–14.
45 Woolsey, C. N., Patterns of sensory representation in the cerebral cortex, *Fed. Proc.*, 6 (1947) 437–441.