3293

Life Sciences, Vol. 23, pp. 2099-2110 N°21 Pergamon Press
Printed in the U.S.A.

DOPAMINE AGONIST PRETREATMENT ALTERS LSD'S ELECTROPHYSIOLOGICAL ACTION FROM DOPAMINE AGONIST TO ANTAGONIST

Greg R. Christoph, Donald M. Kuhn and Barry L. Jacobs

Program in Neuroscience
Department of Psychology
Princeton University
Princeton, New Jersey 08540

(Received in final form September 22, 1978)

Summary

LSD (50 µg/kg, i.v.) significantly depressed the discharge rate of dopamine-containing neurons in the substantia nigra of chloral hydrate anesthetized rats. However, when this same dose of LSD was administered to rats whose nigral cell discharge had been reduced 45% below baseline by d-amphetamine (mean dose = 1.45 mg/kg, i.v.), the discharge rate was significantly increased (typically returning to the pre-amphetamine baseline). A similar pattern was observed when LSD was administered to apomorphine-pretreated animals. Brom-LSD also produced these reversal effects. These effects of LSD resemble those of classical central dopamine antagonists such as haloperidol. We hypothesize that the shift in LSD's action from that of dopamine agonist to antagonist by prior dopamine agonist treatment may be mediated by a conformational shift in the state of the dopamine receptor.

Recent neurochemical evidence indicates that d-lysergic acid diethylamide (LSD) can act as a mixed agonist-antagonist of dopamine (DA) in the central nervous system. LSD stereospecifically stimulates a DA-sensitive adenylate cyclase in the striatum of rats, and also blocks maximal stimulation of this cyclase by DA (1,2). In studies of specific DA receptor binding, LSD displaces radioactively labelled agonist and antagonist ligands, again suggesting that it has affinity for both presumed agonist and antagonist states of the DA receptor (3,4). Furthermore, LSD, like the DA agonist apomorphine, inhibits the accumulation of DOPA that normally follows pretreatment with reserpine, γ-buterolactone, or after cerebral hemisection (5). On the other hand, following central decarboxylase inhibition, LSD enhances striatal DOPA accumulation, an effect which is similar to that caused by the DA receptor antagonist haloperidol (5).

0300-9653/78/1120-2099$02.00/0

In a previous study (6), we reported that LSD (25-50 µg/kg, i.v.) significantly depressed the firing rate of DA-containing neurons in the substantia nigra of anesthetized rats. This LSD-induced reduction in firing rate could be blocked and reversed by low doses of haloperidol. Since the effect of known DA agonists is to reduce the firing rate of DA-containing neurons, and this effect is also blocked and reversed by DA receptor antagonists (7,8), these electrophysiological data supported the view that LSD can act as a DA agonist.

The present investigation examined whether the DA antagonist properties of LSD could also be demonstrated with single-unit recording techniques. Although our previous report demonstrated that LSD pretreatment (200 µg/kg, i.v.) attenuated the depressant effect of the indirect agonist d-amphetamine on DA-containing neurons, this outcome alone is insufficient to draw any definitive conclusions about an antagonistic action of LSD. The present study therefore investigated the ability of LSD to reverse the reduction of unit discharge of DA-containing neurons caused by pretreatment with d-amphetamine or apomorphine. The ability of LSD to reverse the effects of amphetamine pretreatment was also studied in rats whose central serotonin levels had been depleted by prior administration of p-chlorophenylalanine in order to examine whether the DA antagonist-like effects of LSD might be indirectly mediated by its well known effects on serotonin-containing neurons (9,10). Finally, since 2-brom lysergic acid diethylamide (brom-LSD), a nonhallucinogenic congener of LSD, also has the pharmacologic profile of a mixed agonist/antagonist of DA in receptor binding studies (3,4), the effects of brom-LSD on DA-containing neurons, with and without d-amphetamine pretreatment, were also studied.

Methods

Extracellular unit activity in the region of the substantia nigra was studied in Sprague-Dawley rats (230-330 g) of both sexes. Atropine methyl bromide (0.5 mg/kg, i.p.) was administered prior to anesthetization with chloral hydrate (400 mg/kg, i.p.) in order to reduce respiratory congestion. Cannulation of the femoral vein permitted i.v. administration of test drugs. Body temperature was maintained at 35-37°C with a heating pad.

Glass microelectrodes (1-2 µm tip diameter) were filled with 2M NaCl saturated with fast green dye. The electrodes had an impedance of 4-6 megohms measured in vitro at 1000 Hz. A 10 mm^2 area of skull was removed, dura was eliminated, and an electrode was lowered into the region of the substantia nigra [A 1.6-2.2, L 1.5-2.2 (11)] with a hydraulic microdrive system. Amplified signals were monitored on an oscilloscope and stored on magnetic tape. Action potentials activated a Schmitt trigger and the number of spikes was recorded at 1-min intervals with an electronic counter.

Presumed DA-containing neurons were initially identified on-line by three electrophysiological characteristics similar to those described by Bunney et al. (7): (a) the rate of firing was 2-7 spikes/sec.; (b) the pattern of firing was somewhat irregular and a few cells exhibited a clear bursting pattern; and (c) the spike durations were 2 msec or longer (other cells in the region of the substantia nigra had spike durations of 1 msec or less). Only one cell was studied per rat, and drugs were administered only after maintaining a stable baseline firing rate for three min or longer.

LSD alone. For rats that received LSD alone, the initial dose of LSD was 50 µg/kg. With most rats a second injection of LSD (50 µg/kg) was administered 2-8 min (mean = 3.8 min) following the first injection.

AMPH - LSD interaction. While recording the spontaneous activity of a DA-containing neuron, d-amphetamine (AMPH, 0.5 - 1.0 mg/kg) was administered in order to reduce the firing rate by approximately 50%. If necessary, additional injections of AMPH (0.5 - 1.0 mg/kg) were administered at 1-3 min intervals until the 50% rate was reached. The rats received an injection of LSD (50 µg/kg) 2-8 min (mean = 3.6 min) after the last AMPH injection. Most of these rats also received a second injection of LSD (50 µg/kg) 3-6 min later.

Another group of rats was administered p-chlorophenylalanine (PCPA; 400 mg/kg, i.p.) 48 hrs prior to a recording session. AMPH pretreatment and subsequent LSD administration proceeded exactly as described above.

APO - LSD interaction. Apomorphine (APO, 50 - 100 µg/kg) was administered while recording the spontaneous activity of DA-containing neurons and unit discharge immediately ceased for a mean duration of 5.6 min. After this period of no activity the firing rate partially recovered within 2-3 min and stabilized at a mean rate of 74% below the baseline rate. LSD (50 µg/kg) was then administered 2-12 min after attaining this stable reduced rate. The mean time between APO and LSD administration was 13.6 min.

Brom-LSD alone. The effects of brom-LSD (100 µg/kg) on DA-containing neurons were examined. A second 100 µg/kg injection of brom-LSD was administered 2-3 min after the first injection.

AMPH - brom-LSD interaction. DA-containing neurons whose firing rate had been reduced approximately 50% by AMPH, as described above, were also tested with 100 µg/kg of brom-LSD 2-3 min after the last AMPH injection. Most of these neurons were also tested with a second injection of brom-LSD (100 µg/kg) 2-5 min later.

Drugs were obtained from the following sources: d-amphetamine sulphate, Smith, Klein, & French; apomorphine HCl, Sigma: 2-bromlysergic acid diethylamide tartrate U.S.P.H.S.; p-chlorophenylalanine methylester, Pfizer; d-lysergic acid diethylamide tartrate, U.S.P.H.S. Dosages for drugs are expressed as the salt, and all drugs were dissolved in 0.9% saline.

Histological analysis. At the end of a recording session the position of the electrode tip was marked with fast green dye by passing a d.c. current (40 μA, 10 min) through the electrode. The rats then received an overdose of the anesthetic and were perfused intracardially with saline followed by formalin solution. The brains were removed, frozen, sectioned, and mounted on slides in order to determine location of the electrode tip. The zona compacta and zona reticulata of the substantia nigra were visible on moist, unstained sections. All recordings were from neurons within the zona compacta.

Statistical Analysis. For statistical analysis of unit responses to drug administration, the mean discharge rate over the 1-min post-injection period was expressed as a percentage change from the baseline firing rate. To determine the significance of individual unit responses to a given drug, the mean percentage change in firing rate (over the 1-min post-injection period) and standard deviation for seven cells tested with 0.9% saline vehicle was computed (mean % decrease = 3.1, S. D. = 3.3). For individual units tested with drugs, a percentage change from the pre-drug rate that differed from the change caused by saline by more than 2 standard deviations was considered significant $p < 0.05$ level).

Results

LSD alone. Injection of 50 μg/kg of LSD produced a mean decrease of 28.2% (S.E.M. = 6.6, N=28) in the firing rate of presumed DA-containing cells during the first min post-injection. During the 1-min post-injection interval 21 cells fired significantly slower than the baseline rate, 5 cells were unaffected, and 2 units significantly increased their rate above baseline.

For the cells whose firing rate decreased in response to LSD administration, the maximal decrease typically occurred during the first min post-injection. Unit activity rapidly recovered following this maximal decrease, reaching a 50% recovery level in 1-8 min (mean = 3.7 min).

For the 21 DA-containing neurons that were tested with a second 50 μg/kg injection of LSD, the mean firing rate during the 1-min interval immediately preceding the second injection was 15.0% below the original baseline rate. In 18 cases the second injection of LSD significantly reduced the firing rate below the rate that preceded the second injection. The other three cells were not affected by the second injection. The mean firing rate of the 21 cells dur-

ing the 1-min interval after the second injection was 29.4% (S.E.M. = 7.1) below the original baseline rate. Thus, the predominant effect of the second injection of LSD was a slowing of unit discharge rate to about the same level as that caused by the initial injection. As observed after the first injection, rapid recovery of firing immediately followed the maximal slowing caused by the second injection.

AMPH - LSD interaction. In contrast to the generally depressant effects of LSD alone, when 50 µg/kg of LSD was administered to rats whose nigral cell discharge rate had been reduced by 45% (S.E.M. = 4.3) below the baseline by AMPH (mean dose = 1.45 mg/kg), the firing rate significantly increased in 13 of 16 cases. One cell was unaffected by LSD and the discharge rates of two units were significantly reduced.

Considering only the 13 units that responded to LSD with an increase in firing rate, the mean increase was 38% above the rate during the 1-min interval prior to LSD administration (i.e., 7% below the original pre-AMPH baseline). The maximal increase usually occurred during the first 1 min after LSD. Three min after the injection, the mean firing rate was 24% below the original (pre-AMPH) baseline.

Of the ten cells that were tested with a second 50 µg/kg injection of LSD, seven units had responded with an increase in firing rate after the first injection. For these seven cells, the mean firing rate during the 1 min preceding the second injection was 27% below the original (pre-AMPH) baseline. The second LSD injection significantly enhanced the activity of these units so that the mean firing rate exceeded the original baseline by 4% for 2 min post-LSD. Thus, LSD (50 + 50 µg/kg) was able to completely reverse the effect of AMPH in these units. Four min after the second LSD injection the firing rate stabilized at a level 10% below the original baseline. Figure 1 shows the record of a unit for which LSD reversed the suppression of firing rate caused by AMPH pretreatment.

AMPH - LSD interaction in PCPA pretreated rats. In six rats pretreated with PCPA, AMPH (mean dose = 1.8 mg/kg) reduced the firing rate to 46% below the baseline rate. The effect of subsequently administered LSD (50 µg/kg) in these rats was to significantly increase the firing rate in five cells. One cell was unaffected. The average firing rate (excluding the nonresponsive unit) after LSD administration was elevated 22% above the post-AMPH rate (24% below the original baseline). In these five rats, a second 50 µg/kg injection of LSD approximately 4 min after the first injection produced an additional 11% increase in firing rate (i.e., 13% below the original pre-AMPH baseline rate). Thus, LSD was able to reverse the effect of AMPH in PCPA pretreated rats, but the amount of reversal was 15-17% less than that in rats without PCPA pretreatment.

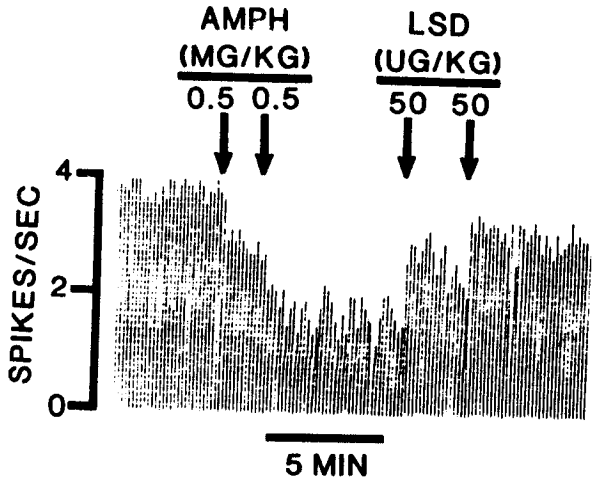

FIG. 1

The height of each line represents the integrated firing rate of a single DA-containing neuron over successive 10-sec intervals. LSD (50 + 50 µg/kg, i.v.) reversed the depressant effect of AMPH pretreatment to 12% below the original baseline rate.

APO - LSD interaction. In rats whose nigral discharge rate had been reduced by a mean of 74.2% (S.E.M. = 3.6) below baseline by APO (50-100 µg/kg), administration of LSD (50 µg/kg) caused a significant increase in firing rate in all cells (N=6) tested. During the 1-min interval post-LSD the mean firing rate increased to a level 33% (S.E.M. = 10.6) below the original (pre-APO) baseline. Half of the cells maintained this rate for 3-4 min and the other cells increased or decreased in rate slightly during this period. Four of these units were tested with a second 50 µg/kg injection of LSD and the mean firing rate was significantly elevated to 15% below the original (pre-APO) baseline during the 1-min post-injection interval. Figure 2 displays the record of a unit for which LSD completely reversed the effect of APO.

Brom-LSD alone; AMPH - brom-LSD interaction. Administration of brom-LSD (100 µg/kg) had no significant effect on the firing rate of 5 of 7 DA-containing neurons and decreased the activity of two others by 15%. A second 100 µg/kg injection of brom-LSD caused the activity of 4 of these 7 cells to significantly slow to 23% (range = 12-42%) below baseline. Three cells remained unaffected.

When 100 µg/kg of brom-LSD was administered to rats whose nigral cell discharge had been decreased 50% by AMPH (mean dose = 1.2 mg/kg), it produced a significant increase in the discharge rate in all six cells tested. During the first min after brom-LSD administration, the mean firing rate was returned to 16% below the

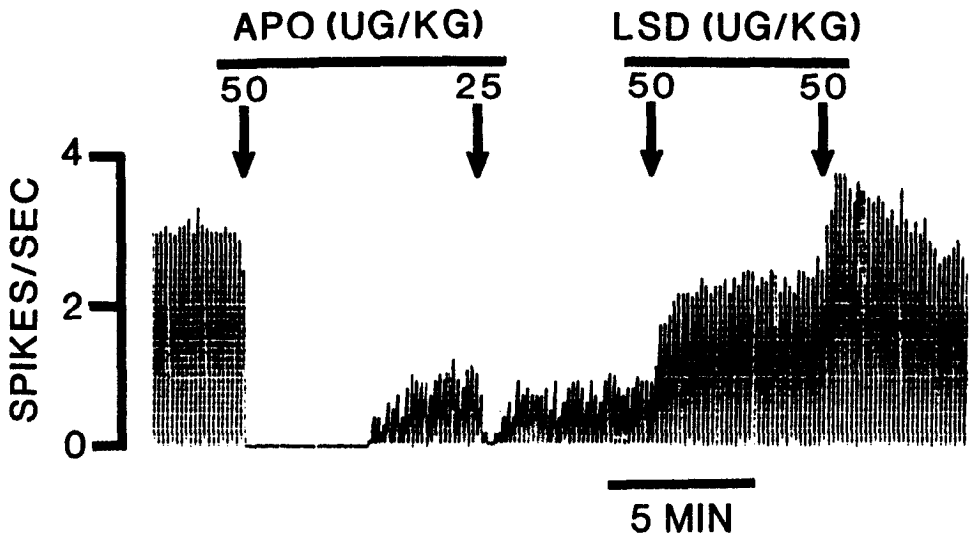

FIG. 2

This single DA-containing neuron was maximally inhibited by APO (50 µg/kg, i.v.) for 4 min. After a rapid and partial recovery a second APO injection caused a transient cessation of unit firing followed by rapid and partial recovery. LSD (50 + 50 µg/kg, i.v.) completely reversed the effect of prior APO administration.

baseline rate. After the second 100 µg/kg brom-LSD injection (N=5) the average firing rate increased to 10% below the original baseline.

Discussion

The effect of LSD on DA-containing neurons was a significant depression of unit discharge rate, which suggests a DA agonist activity (see also 6). The sharp depression and rapid recovery of nigral unit activity produced by LSD was very similar to the previously reported short duration effects of APO on these neurons (8). However, when LSD was administered to AMPH or APO pretreated rats it produced a significant increase in firing rate of DA-containing cells. This reversal of unit firing rate after 50 + 50 µg/kg of LSD consisted of a complete return to the original baseline in most of the AMPH pretreated rats. Since the spontaneous recovery of firing rate after AMPH administration, or after the initial partial recovery phase characteristic of APO administration requires 15-30 min. for 10-25% recovery (7, 12, and unpublished observations from our laboratory), the present quantitative evaluation of LSD's ability immediately to reverse prior agonist treatment is probably not confounded by spontaneous recovery processes.

The effect of LSD following AMPH or APO pretreatment is unlike the effect of known DA agonists following pretreatment with another agonist. For example, the direct acting agonists piribedil and APO exhibit their characteristic depressant effects on DA-containing neurons in AMPH pretreated rats (12, and unpublished observations). The effect of LSD in rats pretreated with DA agonists, on the other hand, closely resembled the action of DA antagonists, which reversed the effects of prior agonists (7, and unpublished observations). Thus, the present finding that LSD reversed the effect of prior DA agonists, in conjunction with our previous data (6), showing that LSD pretreatment significantly attenuated the effectiveness of subsequently administered AMPH, indicates that LSD can also act as a DA antagonist in the CNS. Thus, these data are consistent with neurochemical studies which suggest that LSD is a mixed agonist/antagonist of DA (1-5).

Brom-LSD had a slight depressant effect on a subgroup of DA-containing neurons, suggesting that it may also have some DA agonist properties. This drug, however, was a considerably less effective agonist than LSD. On the other hand, brom-LSD was quite effective in reversing the reduction of nigral cell discharge rate caused by prior AMPH administration with all cells tested, indicating a relatively potent DA antagonist activity. These comparative data on LSD and brom-LSD are also consistent with results from DA-specific receptor binding studies regarding their relative agonist/antagonist potencies (3,4).

In the present study, LSD alone was substantially less effective in reducing nigral cell discharge rates than was a comparable dose of APO, which typically caused a cessation of firing for several minutes. Although the finding that LSD is a less potent agonist than APO is consistent with neurochemical data (3,5), this result is inconsistent with behavioral experiments (13,14) in which LSD is approximately twice as potent a DA agonist as APO. These behavioral studies used a rotational model of DA function in which rats received unilateral injections of 6-hydroxydopamine in the striatum (15). The contralateral rotation caused by LSD and APO in these studies presumably reflects direct DA agonist action on the lesioned side of the brain. Possibly, the greater agonistic potency of LSD over APO in the behavioral experiments is a consequence of denervation supersensitivity. Devervation may abolish the expression of the antagonist action of a mixed agonist/antagonist. In studies such as the present, which employ an intact nigrostriatal preparation, LSD may be a less effective agonist than APO because of its concomitantly expressed antagonist action. Other investigators have also hypothesized that the DA agonist effects of LSD may be much more in evidence in denervated or <u>in vitro</u> preparations than in the intact organism (5,16).

A possible alternative explanation of LSD's antagonist-like activity is that LSD indirectly influences the activity of nigral neurons via an effect on some other neuronal system. For example, systemically administered LSD is known to reduce the firing rate of serotonin (5-HT) - containing neurons located in the midbrain raphe nuclei (9) and to decrease the release of 5-HT in brain areas that receive serotonergic input (17). Since the substantia nigra receives a direct inhibitory serotonergic projection from raphe nuclei (18,19), it is possible that systemic administration of LSD could cause a decrease in amount of inhibitory 5-HT released in nigra. In other words, LSD could disinhibit the DA-containing neurons from presumed inhibitory serotonergic input. Possibly, this disinhibition would be measured as an increase in nigral cell firing rate only when other DA agonists (AMPH, APO) have been previously administered because these other agonists occupy the DA receptors and thereby prevent LSD from exerting its depressant DA agonist effect.

This hypothesis does not seem to be correct for several reasons. First, the present work demonstrated that successive injections of LSD caused successive increments in nigral cell discharge rate in AMPH pretreated rats. The second LSD injection should not have had an effect if the serotonergic mediation hypothesis were correct because the first 50 µg/kg injection is known to maximally inhibit serotonergic neuronal discharge (20,21) and serotonin release (17) far longer than the 3-6 min interval between LSD injections. Thus, the second LSD injection probably had no serotonergic effect beyond that caused by the first injection. Second, brom-LSD is relatively ineffective in depressing the activity of serotonin-containing neurons (20), but was quite effective in reversing AMPH induced depression of nigral activity. The final reason for rejecting the indirect serotonergic mediation hypothesis is that PCPA pretreatment, which is known to cause an 85% depletion of CNS serotonin (22), did not prevent the LSD reversal of AMPH-induced slowing of nigral firing rate.

Another possible explanation of LSD's antagonist-like activity assumes that LSD has a high affinity for the DA receptor, but that it is weak (relative to APO or DA) in stimulating that receptor. Thus, LSD alone should act as a weak agonist and a slight depression of nigral firing rate should occur. In rats pretested with APO or AMPH, on the other hand, LSD molecules would effectively displace the stronger agonist (APO, or DA released by AMPH) molecules from the receptors and a net increase in firing rate would occur. This hypothesis alone, however fails to account for one important feature of the present work, that is, LSD (100 µg/kg) was able to completely reverse the depression of nigral discharge caused by AMPH pretreatment. If LSD were simply a weak agonist with high affinity for the DA receptor, a complete reversal should not have occurred; instead, LSD should

have only been able to cause the cell to fire at a reduced rate, approximately equal to that caused by LSD alone.

The following model is proposed to explain the present results. It is assumed here that the DA receptor exists in one of two interconverting forms: a) an agonist state in which binding of a molecule to the receptor initiates the chain of neuronal events causing excitation (or inhibition), and b) an antagonist state, in which binding to the receptor blocks the initiation of these neuronal events. This assumption is similar to that proposed by Creese et al. (23) for the action of drugs at DA receptors in the CNS. In order to account for the finding that LSD can cause a complete reversal of prior DA agonist pretreatment, it is further assumed that prior agonist treatment causes a net shift of available receptor sites to one favoring the antagonist state. Thus when LSD is administered after agonist treatment, its immediate action will be more purely antagonist-like, rather than agonist-like.

This theoretical formulation of LSD's action at interconverting receptor states is supported by two other experimental results. Recently, Baudry, et. al. (24) reported that binding of ^{3}H-haloperidol is subtantially increased by AMPH pretreatment *in vivo*. This outcome would be expected if the assumption that agonist pretreatment causes a net shift to the antagonist receptor conformation is valid. In an unpublished experiment, J. Welch (personal communication) tested the effect of haloperidol on DA containing neurons in the substantia nigra of rats, with or without AMPH pretreatment (mean AMPH dose = 1.2 mg/kg, i.v.). Haloperidol alone, (0.1 mg/kg, i.v.) caused a mean increase in firing rate of 23%, whereas the same dose of haloperidol in AMPH pretreated rats caused an increase of 85% above the pre-AMPH baseline. This preliminary result also supports the assumption that agonist pretreatment causes a rapid shift in receptor conformation to the antagonist state so that the subsequently administered antagonist is more effective.

In conclusion, the present work, and our previous report about LSD's effects on DA-containing neurons, indicates that LSD is a mixed agonist/antagonist of DA in the CNS. It is suggested that LSD's action as an agonist or antagonist is dependent on the existing conformational state of the DA receptor at the time of LSD administration. Because one of the factors reugulating the conformational state of the receptor may be the level of prior synaptic activity at these receptors, environmental and/or pharmacological factors which affect this activity may influence the hallucinogenic potency of LSD.

Acknowledgements

This research was supported by grant MH 23433 from N.I.M.H. and a N.I.M.H. postdoctoral fellowship to the first author. We thank Smith, Kline & French, Pfizer, and the U.S.P.H.S. for their generous gift of drugs.

References

1. J. BOCKAERT, J. PREMONT, J. GLOWINSKI, A.M. THIERRY, and J.P. TASSIN, Brain Res. 197 303-315 (1976).
2. K. von HUNGEN, S. ROBERTS, and D.F. HILL, Brain Res. 94 57-66 (1975).
3. I. CREESE, D.R. BURT, and S.H. SNYDER, Life Sci. 17 1715-1720 (1975).
4. P.M. WHITAKER and P. SEEMAN, J. Pharm. Pharmac. 29 506-507 (1977).
5. S.-A. PERSSON, Eur. J. Pharm. 43 73-83 (1977).
6. G.R. CHRISTOPH, D.M. KUHN, and B.L. JACOBS, Life Sci. 21 1585-1596 (1977).
7. B.S. BUNNEY, J.R. WALTERS, R.H. ROTH, and G.K. AGHAJANIAN, J. Pharmacol. Exp. Ther. 185 560-571 (1973).
8. B.S. BUNNEY, G.K. AGHAJANIAN, and R.H. ROTH, NATURE NEW BIOLOGY 245 123-125 (1973).
9. G.K. AGHAJANIAN, W.E. FOOTE, and M.H. SHEARD, Science 161 706-708 (1968).
10. J.A. ROSECRANS, R.A. LOVELL, and D.X. FREEDMAN, Biochem. Pharmacol. 16 2011-2021 (1967).
11. J.F.R. KONIG and R.A. KLIPPEL, The Rat Brain, Williams and Wilkins Co., Baltimore (1963).
12. J.R. WALTERS, B.S. BUNNEY, and R.H. ROTH, Advances in Neurology, Vol. 9, (D.B. CALNE, T.N. CHASE and A. BARBEAU, eds.), 273-284, Raven Press, N.Y. (1975).
13. M.E. TRULSON, A.D. STARK, and B.L. JACOBS, Eur. J. Pharm. 44 113-119 (1977).
14. M. PIERI, L. PIERI, A. SANER, M. DaPRADA, and W. HAEFELY, Arch. Int. Pharm. Ther. 217 118-130 (1975).
15. U. UNGERSTEDT, A. AVEMO, E. AVEMO, T. LJUNGBERG, and C. RANJE, Advances in Neurology, Vol. 3 Progress in the Treatment of Parkinsonism (D.B. Calne, ed.), 257-271, Raven Press, N.Y. (1973).
16. W. KEHR and W. SPECKENBACH, Naunyn-Schmiedeberg's Arch. Pharmacol. 301 163-169 (1978).
17. D.W. GALLAGER and G.K. AGHAJANIAN, J. Pharm. Exp. Ther. 193 785-795 (1975).
18. A. DRAY, T.J. GONYE, N.R. OAKLEY, and T. TANNER, Brain Res. 113 45-57 (1976).
19. H.C. FIBIGER and J.J. MILLER, Neuroscience 2 975-987 (1977).
20. G.K. AGHAJANIAN, W.E. FOOTE, and M.H. SHEARD, J. Pharmacol. Exp. Ther. 171 178-187 (1970).
21. M.E. TRULSON, C.A. ROSS, and B.L. JACOBS, Neuropharm. 16 771-774 (1977).

22. M.E. TRULSON and B.L. JACOBS, Eur. J. Pharm. 36 149-154 (1976).
23. I. CREESE, D.R. BURT, and S.H. SNYDER, Handbook of Psychopharmacology, Vol. 10 (L.L. Iversen, S.D. Iversen, and S.H. Snyder, eds.), 37-89, Plenum, N.Y. (1976).
24. M. BAUDRY, M.-P. MARTRES, and J.-C. SCHWARTZ Life Sci. 21 1163-1170 (1977).