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LSD ✓

ELECTROPHYSIOLOGICAL EVIDENCE FOR A DOPAMINERGIC ACTION OF LSD: DEPRESSION OF UNIT ACTIVITY IN THE SUBSTANTIA NIGRA OF THE RAT

Greg R. Christoph, Donald M. Kuhn, and

Barry L. Jacobs

Program in Neuroscience

Department of Psychology

Princeton University

Princeton, New Jersey 08540

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Summary

LSD (25-50 µg/kg, i.v.) significantly decreased the firing rate of 78% of the dopamine-containing neurons in the substantia nigra of chloral hydrate anesthetized rats. In a subgroup of neurons (22%), LSD either had no clear effect or caused a slight excitation. On the other hand, brom-LSD (100 µg/kg, i.v.), a non-hallucinogenic congener of LSD, had no effect on 71% of dopaminergic cells and slightly reduced the firing rate with 29% of the units. Pretreatment with haloperidol (0.1 mg/kg) blocked the inhibitory effects of LSD, and haloperidol injected following LSD reversed its depressive effects. Non-dopaminergic neurons in the region of the substantia nigra typically showed large increases in firing rate in response to LSD administration. The inhibitory effects of LSD on dopamine-containing neurons are probably not attributable to the serotonergic properties of LSD, since 5-methoxy N,N dimethyltryptamine (25-100 µg/kg), which has central serotonergic properties similar to those of LSD, produced exclusively excitatory effects on the firing rate of dopaminergic cells. These electrophysiological results are consistent with recent behavioral and neurochemical data which suggest that LSD can act as a dopamine agonist in the CNS.

A large neurochemical, electrophysiological, and behavioral literature indicates that d-lysergic acid diethylamide (LSD) has

a potent effect on serotonin-(5-HT) containing neurons in the CNS (1-3). On the basis of these studies it has been proposed that the profound psychological effects of LSD may be mediated by its action on this neurochemically identifiable set of neurons (4). Recent behavioral and neurochemical studies, however, support the view that LSD also interacts with dopamine (DA) receptors in mammalian CNS.

In the rotational model of DA function, LSD causes rats to turn contralateral to the side of the brain on which DA nerve terminals in the striatum have been destroyed (5,6). This effect can be blocked by pretreatment with the DA receptor blockers, haloperidol (5) and spiroperidol (6). These results suggest that LSD, like the DA agonist apomorphine, directly stimulates DA receptors. In neurochemical studies, LSD stereospecifically stimulates DA-sensitive adenylate cyclase in the striatum and also blocks DA stimulation of this cyclase which suggests that LSD is a mixed agonist-antagonist of DA (7-9). In addition, studies of DA receptor binding have demonstrated that LSD has a strong affinity for both H^3-DA and H^3-haloperidol binding sites, also suggesting that LSD is a mixed agonist-antagonist of DA (10).

The present study employed extracellular unit recording techniques in order to more directly investigate the dopaminergic properties of LSD. Previous research has demonstrated that DA agonists reduce the spontaneous firing rate of DA-containing neurons in the zona compacta of the substantia nigra (11, 12) and that this effect can be blocked or reversed by haloperidol and other DA receptor blockers (11, 13). We now report that systemic administration of LSD, in low doses, significantly reduces the firing rate of most DA-containing neurons in the zona compacta and that this effect is also blocked or reversed by haloperidol.

We also investigated the possibility that the inhibitory effect of LSD on DA-containing neurons was mediated by LSD's serotonergic properties. High concentrations of 5-HT have been found in the zona compacta (14), and microiontophoretic application of 5-HT in the zona compacta is reported to slightly reduce the firing rate of DA-containing neurons (15). The reduction in firing rate of DA-containing cells caused by LSD in our experiments might therefore be due to LSD's action as a 5-HT agonist on DA-containing neurons. We investigated this possibility by comparing the effects of LSD with those of a known serotonergic agonist (5-methoxy N,N dimethyltryptamine: 5-MeODMT) (16).

Methods

Units in the region of the substantia nigra were studied in male and female Sprague-Dawley rats (230-330 g). 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 permit-

ted i.v. administration of test drugs. Body temperature was maintained at approximately 35°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 (17)) 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.

The electrophysiological effects of LSD were examined on 45 presumed DA-containing cells. Only one cell was studied per rat, and drugs were administered only after achieving a stable baseline firing rate for 3 min. or longer. The initial dose of LSD was either 25 μg/kg or 50 μg/kg; subsequent doses of LSD (25-100 μg/kg) were administered at 3-6 min. intervals. The dose of a subsequent injection was equal to the current cumulative dosage level. A cumulative dose of 200 μg/kg was reached with 25 cells.

Since the systemic administration of d-amphetamine inhibits dopaminergic cells (11), d-amphetamine (0.5-1 mg/kg, i.v.) was administered after LSD to determine if it would also inhibit the cells in this study. Subsequent injections of d-amphetamine were made at 2-5 min. intervals until 50% suppression of firing rate was attained or until 8 mg/kg had been administered. Some of the cells that had been tested with LSD were subsequently tested with a low dose of haloperidol (0.1-0.2 mg/kg) in order to determine whether the effects of LSD could be reversed by this DA antagonist. Other rats received haloperidol (0.1 mg/kg) 4-8 min. prior to administration of LSD in order to determine if the LSD effects could be blocked by this DA antagonist.

Presumed DA-containing neurons were also tested with 5-MeODMT (25-100 μg/kg) and with 2-brom-lysergic acid diethylamide (brom-LSD: 100 μg/kg, i.v.) in order to compare the effects of these drugs with those of LSD. Control cells in the region of the substantia nigra, which did not meet the electrophysiological criteria for DA-containing neurons, were tested with LSD and with d-amphetamine and/or haloperidol. DA-containing cells were tested with saline vehicle (n = 7) or acidified saline vehicle (pH =3.0, n = 4) prior to drug treatment. The volume of the vehicle injections approximated the volume of the drug injections.

At the end of a recording session the position of the electrode tip was marked with fast green by passing a d.c. current (40 μA, 10 min) through the electrode. Rats then received a lethal dose 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 placement of the electrode tip. The zona compacta and zona reticulata of the substantia nigra were visible on moist, unstained sections.

Presumed DA-containing neurons were initially identified on-line by three electrophysiological characteristics similar to those noted by Bunney et al. (11). First, the rate of firing was 2-7 spikes/sec. Second, the pattern of firing was somewhat irregular and a few cells exhibited a clear bursting pattern. Third, 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).

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 of 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 the cells tested with saline and with acidified saline was computed (saline: mean % decrease = 3.1, S. D. = 3.3; acidified saline: mean % increase = 2.9, S. D. = 3.1). For individual units tested with drugs, a percentage change from baseline that differed from the mean of the respective vehicle by more than 2 standard deviations was considered significant ($p < 0.05$ level).

Drugs were obtained from the following sources: d-amphetamine sulphate, Smith, Klein, & French; 2-brom-lysergic acid diethylamide tartrate U.S.P.H.S.; haloperidol, McNeil Laboratories; d-lysergic acid diethylamide tartrate, U.S.P.H.S.; 5-methoxy N,N dimethyltryptamine, Sigma Chemical Co. Dosages for drugs are expressed as the salt, if appropriate, and all drugs were dissolved in 0.9% saline (acidified to pH 3.0 with HCl for haloperidol and 5-MeODMT).

Results

Administration of 25 µg/kg (n = 18) or 50 µg/kg (n = 27) caused an immediate and statistically significant reduction in

TABLE 1
Firing Rate of Presumed DA-Containing Cells after Administration of LSD

NUMBER OF CELLS

LSD Dose	Percentage Change from Baseline Firing Rate								
	Decrease						Increase		
(µg/kg)	100-80	80-60	60-40	40-20	20-10	10-0	0-10	>10	N
25	1	3	2	3	6	2	1	0	18
50	4	2	3	6	5	4	2	1	27

firing rate of 78% of presumed DA-containing neurons. Seven units

(15%) were not affected and 3 units (6%) increased in rate slightly. Table 1 presents the number of cells that fell into different categories of percentage change from baseline firing rate during the 1-min post-injection period. Table 1 shows that a slowing of unit discharge was the predominant effect of LSD and that the amount of slowing varied considerably from cell to cell. Ten units (22%) abruptly stopped firing for 5-15 sec and immediately began recovery toward the original baseline. Figure 1 shows the record of such a unit. .The rapid recovery was observed in about 80% of the 35 units whose firing rate was significantly

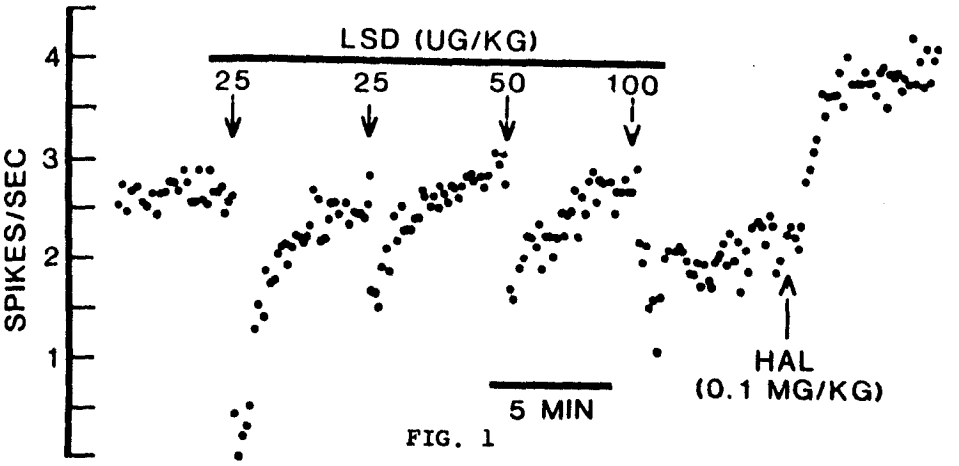

FIG. 1

Effects of LSD (i.v.) and haloperidol (i.v.) on the spontaneous firing rate of a single dopaminergic cell in the zona compacta of the substantia nigra. The data points represent the firing rate computed for successive 10-sec intervals.

slowed by LSD. For the cells that rapidly recovered, a mean of 3.6 min. (range 1-7 min.) was required for a 50% recovery.

Of the cells whose firing rate was significantly reduced by the initial injection of LSD, 26 cells were tested with a second equivalent dose of LSD 3-6 min. later. Tachyphylaxis, that is, reduced effectiveness of the second injection, was evident with 50% of these cells. Tachyphylaxis occurred with all of the units (n = 5) whose unit discharge briefly ceased in response to the initial injection. With these latter cells, the second injection caused much less reduction in firing rate (mean = 42% below baseline) than that caused by the initial injection (mean = 72% below baseline). Figure 1 illustrates the diminished effectiveness of the second injection with such a unit.

After a cumulative dose of 200 µg/kg of LSD had been administered (N = 25), the average stabilized firing rate was 23% below the baseline rate. The rate of three cells significantly exceeded the baseline rate by about 16%, 20 cells were significantly slowed

and two cells were unaffected.

A subgroup of the cells that were tested with LSD were subsequently tested with d-amphetamine (N = 17). These tests were done in order to confirm that the cell under study was a DA-containing neuron and to determine the dose of d-amphetamine required to produce a 50% decrease in firing rate. Administration of d-amphetamine was found to reduce the rate of all 17 units and this is the characteristic effect of d-amphetamine on DA-containing units (11). In rats that had received 200 µg/kg of LSD (N = 13), the average dose of d-amphetamine that was required to produce a 50% reduction of the pre-LSD firing rate exceeded 4.2 mg/kg. Four cells still fired faster than the 50% level even with 8 mg/kg of d-amphetamine; these cells, however, fired 15-30% slower than they had fired after LSD. For 12 units that were not previously tested with LSD, the average dose of d-amphetamine that caused 50% suppression of firing rate was 1.2 mg/kg. This dose of d-amphetamine is significantly smaller than that required when LSD was previously administered (t-test, $p < .001$). Thus LSD pretreatment attentuated the effectiveness of a known DA agonist.

Ten of the cells whose firing rate had been reduced by LSD were subsequently tested with the DA receptor blocker haloperidol (0.1-0.2 mg/kg). Haloperidol increased the firing rate of all 10 cells and the rate typically exceeded the pre-LSD baseline (see Figure 1). Thus, haloperidol reversed the suppression of firing rate caused by LSD, and the effect of haloperidol was similar to that reported in other studies of DA-containing neurons (11).

Presumed DA-containing neurons (N = 8) were tested with a low dose of haloperidol (0.1 mg/kg) first and were then tested with LSD (50 µg/kg) in order to examine whether the effects of LSD could be blocked by this DA antagonist. With one exception, the firing rate of these cells increased in response to haloperidol to about 10% above baseline, and none of these cells responded with a reduction in rate when LSD was given. For two of the units, LSD significantly increased the rate by about 20% and the other cells showed a slight increase or no effect. Apparently, haloperidol blocked the inhibitory effect of LSD, but it did not block the excitatory effect of LSD that was occasionally observed when LSD alone was given.

In contrast to the effects of LSD, administration of 5-MeODMT (25-100 µg/kg) caused every presumed DA-containing neuron (N = 7) to increase in rate. The average increase was 27% above baseline (range = 8%-78%) and was statistically significant with 6 of the cells. For two cells a second 50 µg/kg injection of 5-MeODMT was given a few min. after the initial injection (cumulative dose = 100 µg/kg) and the firing rate increased even further. When apomorphine (50 µg/kg) was administered after 5-MeODMT (N = 3), unit discharge ceased for 1-4 min. and the firing rate then quickly recovered to 25%-50% below the baseline rate. This effect of apomor-

phine is similar to that reported in other studies of apomorphine's effects on DA-containing neurons (12, 13), thereby confirming the dopaminergic identity of the cells.

Administration of brom-LSD (100 µg/kg, n = 7) had no effect on 5 presumed DA-containing cells and slowed the firing rate of 2 cells by about 15%. Thus, this dose of brom-LSD was less effective than lower doses of LSD.

The effects of LSD on cells in the region of the substantia nigra that were presumably not DA-containing neurons were unlike the LSD effects reported above. The baseline firing rates of these control units were either much slower (0.75 spikes/sec) or much faster (9-12 spikes/sec) than the presumed DA-containing units, and the spike durations were about 1 msec. For eight of the ten control cells, LSD (25-50 µg/kg) increased the rate of firing, often to greater than twice the baseline rate. The two other control units were unaffected. Administration of d-amphetamine (1-6 mg/kg) after LSD further increased the firing rate in five cells and had no clear effect in two others. Haloperidol (0.1-0.4 mg/kg) either had no effect (N = 3) or reduced the firing rate (N = 3). Apparently, only DA-containing neurons in the region of the substantia nigra consistently show a reduction in firing rate in response to LSD.

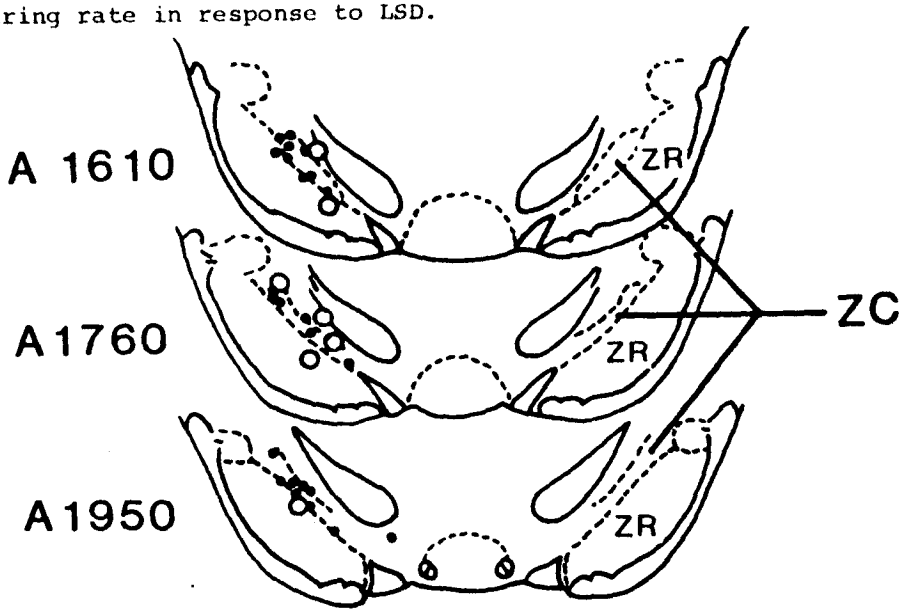

Fig. 2

Electrode tip placements for 23 of the presumed dopaminergic cells (solid circles) and for seven of the control cells (open circles). ZC and ZR refer to the zona compacta and zona reticulata, respectively. The anterior coordinates, in microns, refer to successive sections traced from König and Klippel (17).

Most of the cells that had the electrophysiological and pharmacological characteristics of DA-containing neurons were located within, or on the borders of, the zona compacta of the substantia nigra (Figure 2). A few presumed DA-containing cells were located more medially, that is, in the ventral tegmental area. Dopaminergic cell bodies are also known to exist in this more medial (A10) group of neurons (18). The locations of the control cells were either on the borders of the zona compacta, or they were dorsal or ventral (zona reticulata) to the zona compacta. There were no obvious anatomical differences between the presumed DA-containing neurons that were strongly inhibited, unaffected, or slightly excited by LSD.

Discussion

The present data, indicating that low doses of LSD (25-50 µg/kg) significantly depress nigral unit activity, complement the behavioral and neurochemical data (5-10) which suggest that LSD is a potent direct-acting DA agonist. The cells studied had electrophysiological, pharmacological, and anatomical properties of DA-containing neurons (11). DA agonists are known to reduce the firing rate of these neurons, and reduction of firing rate was the most frequently observed effect of LSD. Furthermore, the DA antagonist haloperidol was found to block and reverse the reduction in firing rate caused by LSD. The LSD-induced suppression of firing rate was not due to a general impairment of neural function since control cells in the region of the substantia nigra typically increased their firing rate in response to LSD administration. Nor are these effects of LSD attributable to its peripheral actions, since higher doses of brom-LSD had little or no effect on the activity of nigral cells (19).

The effects of LSD were similar in two other ways to the electrophysiological effects of known DA agonists, apomorphine and piribedil (12, 13). First, the LSD-induced suppression showed a rapid recovery. Second, LSD pretreatment attenuated the effectiveness of a subsequently administered dopaminergic compound, d-amphetamine. It is possible that these phenomena may be attributable to the mixed DA agonist-antagonist properties of LSD which have been inferred from neurochemical studies (7-10). In this regard it is noteworthy that the DA agonist apomorphine has also been found to have some potential as a DA antagonist (10).

Walters et al. (13) demonstrated that prior treatment with apomorphine attenuates the inhibitory effect of subsequently administered apomorphine on dopaminergic unit activity (tachyphylaxis). Unlike, apomorphine, prior administration of LSD did not consistently attenuate the effectiveness of a second, equivalent dose of LSD. Tachyphylaxis was consistently observed only with those cells whose unit discharge briefly ceased in response to the

initial injection. It is possible that the units that were most sensitive to LSD represent a pharmacologically distinct subclass of DA-containing units.

The contralateral rotation effects of LSD in behavioral experiments indicate that LSD directly stimulates DA receptors and does not act indirectly, for example, by causing the release of endogenous DA (5,6). Dopaminergic receptors are probably located presynaptically, that is, on the DA-containing neurons, as well as postsynaptically, that is, on target neurons in the striatum (20, 21). Thus, the site of action of LSD could be either pre- or postsynaptic, or both. If the principal site of action were postsynaptic, the reduction in firing rate we observed would presumably by mediated by a negative-feedback striato-nigral pathway (20).

The possibility that LSD's inhibitory effects on DA-containing neurons were mediated by its serotonergic properties does not seem likely for two reasons. First, a low dose of the specific DA receptor antagonist haloperidol (0.1 mg/kg) blocked the inhibitory effect of LSD. Second, the effects of 5-MeODMT and those of LSD were qualitatively different. Whereas LSD reduced the firing rate of most DA-containing neurons, 5-MeODMT increased the firing rate of most dopaminergic units tested. If the LSD-induced reduction of firing rate of DA-containing neurons were due to a 5-HT agonistic action of LSD, then 5-MeODMT, which, like LSD, directly stimulates central 5-HT receptors (16), should have had effects on dopaminergic units similar to those of LSD.

A possible explanation for the increase in firing rate caused by 5-MeODMT is that this drug reduced impulse flow in 5-HT-containing neurons and thereby released DA-containing neurons from serotonergic inhibition. In support of this hypothesis, recent anatomical (22) and electrophysiological evidence (23) suggests that DA-containing neurons in the substantia nigra receive an input from cells in the raphe nuclei, in which the cell bodies of serotonergic neurons predominately are located. This input is probably inhibitory (23). Low doses of 5-MeODMT (20 µg/kg, i.v.) have been found to reduce unit discharge of serotonergic neurons by about 75% (24). This effect of low doses of systemically administered 5-MeODMT on impulse flow in serotonergic neurons is probably much more important than direct stimulation of postsynaptic 5-HT receptors on the dopaminergic target cells. Like LSD (2), the 5-HT agonist effects of microiontophoretic 5-MeODMT on cells postsynaptic to serotonergic neurons are much weaker than the effects of 5-MeODMT on 5-HT-containing neurons (G. K. Aghajanian, personal communication). Since the major effect of systematically administered 5-MeODMT is probably a reduction of impulse flow in 5-HT-containing neurons, the consequent reduction in release of inhibitory 5-HT in the substantia nigra is hypothesized to be the mechanism of the effects of 5-MeODMT on dopaminergic cells.

LSD is also known to reduce unit discharge of 5-HT-containing neurons (2), and, therefore, should also release DA-containing neurons from serotonergic inhibition. The additional DA agonist action of LSD, however, presumably counteracts and overrides this release from serotonergic inhibition. Thus, LSD may have two opposing actions on DA-containing neurons which jointly determine how a given cell will respond to LSD. Accordingly, we speculate that the wide variation of the effects of LSD on dopaminergic cells that we observed may correspond to variation in serotonergic input. This hypothesis of the effects of LSD on DA-containing neurons may explain why haloperidol blocked only the inhibitory effects of LSD--release from serotonergic inhibition was presumably not altered by blockade of DA receptors so that only excitation or no effect was observed. The hypothesized release from serotonergic inhibition may also contribute to the rapid recovery of DA unit activity following LSD administration and may be partly responsible for LSD's attentuation of the effectiveness of d-amphetamine.

Two other studies (11, 25) have briefly reported that LSD, in doses similar to those employed in the present study, had no effect on the firing rate of DA-containing neurons. In our more extensive investigation we also found some units that were not responsive to LSD, but the predominant effect was a depression of dopaminergic unit activity. There are three differences between the present study and previous work. First, in the present study the rats were pretreated with a peripherally acting cholinergic blocker, atropine methyl bromide, to control respiratory congestion. Second, body temperature was maintained at approximately 35°C rather than 36-37°C used in the other studies. Third, the cells in the present study fired at a slightly lower rate (2-7 vs. 3-9 spikes/sec) and only occasionally displayed a bursting pattern. Since administration of the anesthetic chloral hydrate causes dopaminergic cells to increase their rate and burst (11), the rats may have been less deeply anesthetized than the rats in the other studies. We do not know the extent to which these factors account for the differences in our results.

In conclusion, our work supports the view that LSD, in low doses, acts as a DA agonist. However, it is not necessary for drugs to be DA agonists in order to have hallucinogenic or psychotomimetic properties. For example, 5-MeODMT and psilocin are both reported to be hallucinogenic (26, 27), and neither of these drugs have DA agonist properties (6). Possibly, the ability of a drug to directly or indirectly stimulate DA receptors is one determinant of hallucinogenic potency. This hypothesis was suggested by previous behavioral studies of a variety of hallucinogens (6) in which it was found that hallucinogenic potency, as determined by animal and human studies (see 28), is positively correlated with a drug's ability to act as a DA agonist. Thus, we speculate

that drugs which reduce impulse flow in serotonergic neurons, and, in addition, act as DA agonists are the most potent hallucinogenic compounds.

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