*Neuropharmacology* Vol. 22, No. 6, pp. 669–676, 1983

# COMPARISON OF THE EFFECTS OF LSD AND LISURIDE ON A10 DOPAMINE NEURONS IN THE RAT

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(*Accepted* 22 *November* 1982)

**Summary**—Extracellular single-unit recording techniques were used to compare the effects of *d*-lysergic acid diethylamide (LSD) and its non-hallucinogenic congener lisuride hydrogen maleate (LHM) on the activity of dopamine (DA) neurons in the A10 region of the rat ventral tegmental area. Lisuride hydrogen maleate potently suppressed the firing rates of A10 DA cells ($ID_{50} = 0.021$ mg/kg). The DA antagonist haloperidol prevented, but did not reverse, the effect of lisuride. In addition, the DA agonist apomorphine was unable to suppress further the firing rates of A10 DA cells that had been partially suppressed by small doses of lisuride. These results suggest that lisuride acted as a non-competitive or irreversible DA agonist. In contrast to lisuride, LSD exerted mixed effects on A10 DA cells, partially depressing the firing rates of 54% of the cells tested, increasing the firing rates of 23% of the cells and exerting no effect on the other 23%. The response of a particular A10 DA cell to administration of LSD was dependent upon its baseline firing rate. Haloperidol readily reversed the LSD-induced partial suppression of the firing of A10 DA cells. Also, LSD effectively reversed apomorphine-induced suppression and increased the doses of apomorphine required to suppress firing of A10 DA neurons. These results suggest that, in addition to its weak DA agonist effects, LSD also exerted partial DA antagonist effects. Pharmacological and physiological manipulations of serotonergic neuronal systems failed to implicate a role for serotonin in the effects of LSD and lisuride on A10 DA neurons. These qualitative and quantitative differences between the effects of LSD and lisuride on A10 DA neurons suggest that the potent DA agonist actions of lisuride may contribute to its lack of hallucinogenic potential.

Key words: LSD, lisuride hydrogen maleate, 5-methoxydimethyltryptamine, A10 dopamine neurons, hallucinogens.

Hypotheses regarding the mechanism(s) by which *d*-lysergic acid diethylamide (LSD) and other hallucinogenic drugs exert their unique behavioral effects have emphasized alterations in the activity of central serotonin (5-hydroxytryptamine; 5-HT) systems (for recent reviews see Freedman, 1981; Freedman and Boggan, 1981). Specifically, it has been proposed that the ability of LSD to act as an agonist at either presynaptic or postsynaptic 5-HT receptors (or both) may be responsible, in large part, for the perceptual and behavioral manifestations of the LSD experience (e.g. see Appel, White and Holohean, 1982; De-Montigney and Aghajanian, 1977; Freedman, 1981; Haigler and Aghajanian, 1974). There have also been reports that LSD is an agonist at central dopamine (DA) receptors (Burt, Creese and Snyder, 1976; Christoph, Kuhn and Jacobs, 1977; DaPrada, Saner, Burkard, Bartholini and Pletscher, 1975; Kelley and Iversen, 1975; Pieri, Pieri and Haefely, 1974; Von Hungen, Roberts and Hill, 1979) which has led to proposals that this action may contribute to the hallucinogenic effects of LSD (Christoph *et al.*, 1977; Jacobs, Trulson, Stark and Christoph, 1977; Nichols, 1976; Pieri *et al.*, 1974).

In recent years, it has been found that lisuride hydrogen maleate (LHM), a non-hallucinogenic structural congener of LSD (Horowski, 1978), exerts neuropharmacological actions that are strikingly similar to those of LSD, particularly with respect to their effects on 5-HT-containing neuronal systems (Kehr, 1977; Pieri, Kellar, Burkard and DaPrada, 1978; Rogawski and Aghajanian, 1979; Rosenfeld and Makman, 1981; Silbergeld and Hruska, 1979; Walters, Baring and Lakoski, 1979b). While some investigators have cited this evidence as seriously questioning the 5-HT hypothesis of hallucinations (Pieri *et al.*, 1978), others have strived to identify differences between the neuropharmacological actions of LSD and lisuride which might be essential for hallucinations (McCall and Aghajanian, 1980; White and Appel, 1982a).

The most often noted differences between the neuropharmacological effects of LSD and lisuride have involved actions on dopamine (DA)-containing neuronal systems (for review see Freedman and Boggan, 1981). For example, lisuride is more potent than LSD at decreasing turnover of DA (Kehr, 1977; Pieri *et al.*, 1978), inhibiting the binding of radiolabelled DA ligands to striatal homogenates (Seeman, 1981), suppressing the activity of DA-containing neurons in the substantia nigra (Walters *et al.*, 1979a,b), eliciting stereotyped behavior in rats

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(Horowski, 1978) and mimicking the discriminable effects of the DA agonist apomorphine (Holohean, White and Appel, 1982). Moreover, the greater potency of lisuride at DA receptors is primarily responsible for the different discriminable "states" produced by lisuride and LSD in the rat (White and Appel, 1982a,b). Accordingly, differences in DA-mimetic activity may also contribute to differences in the hallucinogenic potential of LSD and lisuride.

Comparative studies of the effects of LSD and lisuride on DA systems have been mostly limited to the nigro-striatal DA system. Perhaps of greater relevance for hypotheses of hallucinations are the mesolimbic and mesocortical DA systems which arise primarily from the A10 DA neurons in the ventral tegmental area (VTA). These DA systems have been implicated in various affective and cognitive aspects of behavior (Oades, 1982; Simon, Scatton and LeMoal, 1980) and are thought to be dysfunctional (hyperactive) in schizophrenic disorders (Matthysse, 1973; Stevens, 1973). Since acute administration of LSD, but not lisuride, can mimick the primary symptoms of schizophrenia (cognitive and affective disturbances, hallucinations), it is possible that any differences between the actions of LSD and lisuride on mesolimbic and mesocortical DA neurons may be particularly relevant to the different subjective effects produced by these ergots. Therefore, in the present experiments, extracellular single-unit recording techniques were used to compare the effects of LSD and lisuride on A10 DA neurons in the rat.

## METHODS

### *Subjects*

Male Sprague–Dawley rats (Sasco, St Louis, MO) weighing between 200 and 300 g were used in all experiments. The rats were housed in groups of 2–4/cage in a room with constant temperature (21–23°C) and humidity (40–50%) on a 12 hr light/dark cycle (7:00 a.m.–7:00 p.m.).

### *Procedures*

For single unit recording, rats were anesthetized with chloral hydrate (400 mg/kg i.p.) and mounted in a stereotaxic apparatus (David Kopf Instruments). Additional injections of chloral hydrate (as needed) and all test compounds were administered through a 25 gauge needle inserted in a lateral tail vein. To record A10 DA cells in the ventral tegmental area, a small burr hole was drilled with its centre at 3.0 mm anterior (A) to lambda and 0.5 mm lateral (L) from the midline. Micropipettes were broken back (under a microscope) to approx. 1 $\mu$m at the tip and were filled with 2 M NaCl saturated with 1% Fast Green dye (Fisher). *In vitro* impedances of these electrodes were typically 3–6 MΩ measured at 60 Hz. The micropipettes were lowered through the burr hole into the ventral tegmental area (defined as 6.0–8.5 mm below the dura) with a hydraulic microdrive system. Standard extracellular single-unit recording techniques were used as previously detailed (Wang, 1981; White and Wang, 1983). Briefly, electrical signals were passed through a high impedence amplifier, displayed on an oscilloscope and fed into a window discriminator (Fintronics WDR 420) which was set such that the standard output was triggered by individual action potentials. Integrated rate histograms generated by the analog output of the window discriminator were plotted on a polygraph recorder (Gould 220). Electrical signals from the oscilloscope drove an audiomonitor (Grass AM8).

The A10 DA neurons were identified by criteria previously shown to be characteristic of DA neurons in the ventral tegmental area (Bunney, Walters, Roth and Aghajanian, 1973; Deniau, Thierry and Feger, 1980; German, Dalsass and Kiser, 1980; Wang, 1981; White and Wang, 1983; Yim and Mogensen, 1980). These criteria include: (1) either a slow regular firing pattern or a slow bursting pattern with progressively decreasing spike amplitude (rates: 0.5–8.0 spikes/sec); (2) biphasic or triphasic waveforms consisting of a predominant positive, then negative spike frequently followed by a third positive component; and (3) relatively long duration action potentials (> 2.5 msec) and a low pitch sound when monitored on an audio amplifier. Baseline firing rates were determined for at least 3 min before testing of drugs. All drugs were injected on a regimen in which each dose doubled the previously administered dose. Only one cell was recorded per rat. At the end of recording, the electrode sites were marked by passing a 25 $\mu$A cathodal current through the electrode barrel for 15 min which deposited a discrete spot of green dye. The rats were then perfused with 0.9% saline followed by 10% buffered formalin. Recording sites were verified on serial coronal sections which were cut at 50 $\mu$m intervals, stained with cresyl violet and counterstained with neutral red.

In some cases, the effects of LSD and lisuride on A10 DA neurons were examined in rats with transections of the brain to determine whether changes in afferent input to the A10 DA cells might be responsible for the observed effects of LSD and lisuride. Thin glass microknives were made by cutting off a segment of microscope slide slip covers (De Jong and Palkovits, 1976). Just before recording began, transections were made at A 5.5 and A 2.0 to prevent communication to the ventral tegmental area from structures in the forebrain and posterior brainstem. Following recording, the transections were verified histologically on serial saggital sections.

### *Drugs*

Lisuride hydrogen maleate (Schering AG), *d*-lysergic acid diethylamide bitartrate (NIDA), and ketanserin HCl (Janssen) were dissolved in 0.9% NaCl. Doses of these drugs refer to the weights of the salts. Haloperidol (McNeil) was dissolved in 0.01 M citric acid and the pH was adjusted to 7.2 with NaOH. 5-Methoxy-*N*-*N*-dimethyltryptamine

(5-MeODMT, Regis) was dissolved in a minimum amount of tartaric acid, diluted with 0.9% NaCl and the pH was adjusted to 6.8 with NaOH. Metergoline (Farmitalia) was dissolved in 1.0% ascorbic acid (pH adjusted to 6.8); this antagonist was injected 1 hr before recording (either 1.5 mg/kg i.p. or 0.5 mg/kg i.v.) because of its slow onset and long duration of action (Wang and Aghajanian, 1978).

## RESULTS

### *Effects of lisuride on A10 DA neurons*

Lisuride hydrogen maleate markedly suppressed the firing rates of all 17 A10 DA neurons that were tested; the $ID_{50} \pm SEM$ for this effect was $0.021 \pm 0.003$ mg/kg (Fig. 1). Of the 12 DA cells that were tested for complete dose–response effects, nine were totally inhibited by lisuride; the mean dose ($\pm$SEM) of lisuride required for complete suppression of firing of these cells was $0.052 \pm 0.008$ mg/kg. The suppression of firing of A10 DA cells by lisuride was typically of long duration. Three cells observed for recovery had not returned to their baseline firing rate after 60 min. The dopamine antagonist haloperidol was unable to reverse the lisuride-induced suppression (Fig. 2A) even in large doses (3.0 mg/kg, $n = 8$). However, when administered before lisuride, haloperidol (0.05–0.63 mg/kg i.v., $n = 6$) completely prevented the inhibitory effects of lisuride on A10 DA neurons (Fig. 2B). In all six of these cells, large doses of lisuride (>0.1 mg/kg) caused slight increases in firing rate (mean increase to 114% of baseline). If lisuride was administered in doses that only partially suppressed the firing of an A10 DA neuron, even large doses (>0.5 mg/kg) of the DA agonist apomorphine were unable to further suppress the firing of the cell (Fig. 2C). When A10 DA cells were suppressed by apomorphine, lisuride failed to reverse the suppression ($n = 3$).

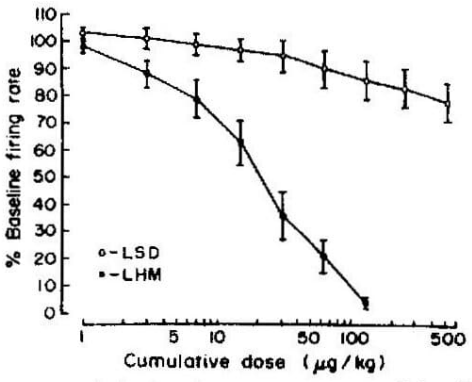


Fig. 1. Cumulative log dose–response curves of the effects produced by increasing intravenous doses of lisuride (LHM) or LSD on the firing rates of A10 dopamine neurons in the rat ventral temental area. Data points for LSD represent the mean of 13 rats except for the last data point ($n = 8$). Data points for lisuride represent the mean of 17 rats except for the last two data points ($n = 14$ and 12, respectively). Vertical bars represent standard errors of the mean.

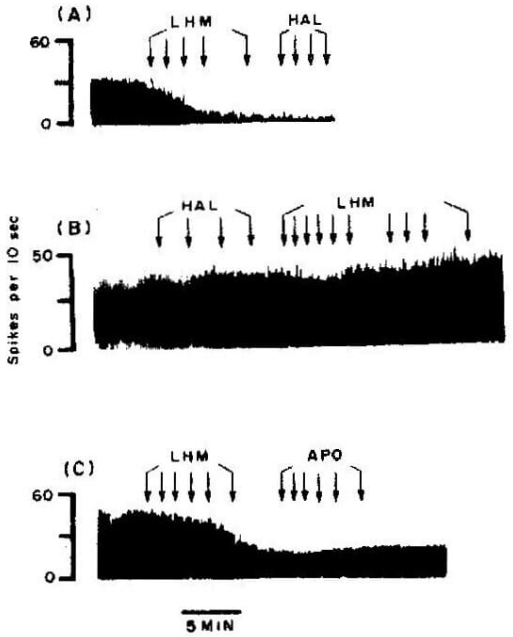


Fig. 2. Effects of lisuride hydrogen maleate (LHM) on the firing rates of A10 dopamine (DA) neurons in the rat ventral tegmental area. (A) Typical suppression of the firing rate of an A10 DA neuron produced by increasing intravenous doses of lisuride (0.001, 0.002, 0.004, 0.008 and 0.016 mg/kg; total dose, 0.031 mg/kg) and the inability of haloperidol (HAL) (0.05, 0.1, 0.2 and 0.4 mg/kg i.v.; total dose, 0.75 mg/kg) to reverse the suppression. (B) Prevention of the rate-suppressant effects of increasing intravenous doses of lisuride (0.001–0.512 mg/kg; total dose, 1.023 mg/kg) on an A10 DA neuron by pretreatment with haloperidol (0.005, 0.01, 0.02 and 0.04 mg/kg; total dose, 0.075 mg/kg i.v.). (C) Partial suppression of the firing rate of an A10 DA neuron produced by increasing intravenous doses of lisuride (0.001–0.032 mg/kg; total dose, 0.063 mg/kg) and the failure of apomorphine (APO; 0.001–0.032 mg/kg; total dose, 0.063 mg/kg i.v.) to further suppress the firing rate of the cell.

### *Effects of LSD on A10 DA neurons*

In contrast to lisuride, LSD produced mixed effects on A10 DA neurons. Of 13 DA cells tested with LSD, 7 (54%) were suppressed (Fig. 3A), 3 (23%) were transiently excited (Fig. 3B) and 3 (23%) were unresponsive. Of the 3 cells that were excited by LSD, the average increase was to 118% of baseline (maximum increase: 144% of baseline). Of the 7 cells that were suppressed by LSD, only 3 were suppressed to 50% of baseline firing rate and none were completely suppressed; the mean dose ($\pm$SEM) required for suppression was $0.037 \pm 0.007$ mg/kg. The maximum suppression was to 44% of baseline at a total dose of 0.511 mg/kg. When the effects on all cells were averaged, the maximum suppression was only to 78% of baseline (Fig. 1); when only those cells ($n = 7$) that were suppressed were averaged, the maximum suppression was only to 60% of baseline. Thus, no $ID_{50}$ value could be calculated. Haloperidol rapidly reversed the LSD-included suppression (Fig. 3A). This reversal contrasted with spontaneous recovery which

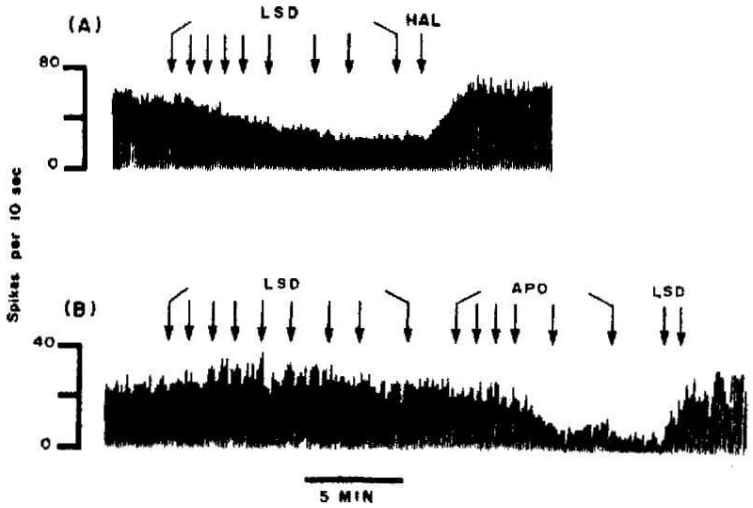


Fig. 3. Effects of LSD on the firing rates of A10 dopamine (DA) neurons in the rat ventral tegmental area. (A) Partial suppression of the firing rate of an A10 DA neuron produced by increasing intravenous doses of LSD (0.001, 0.002, 0.004, 0.008, 0.016, 0.032, 0.064, 0.128 and 0.256 mg/kg; total dose, 0.511 mg/kg) and the rapid reversal of this effect by haloperidol (HAL; 0.05 mg/kg i.v.). (B) Increases in the firing rate of an A10 DA neuron produced by increasing intravenous doses of LSD (0.001–0.256 mg/kg; total dose, 0.511 mg/kg); the subsequent partial suppression of the firing rate of the cell by increasing intravenous doses of apomorphine (APO; 0.001–0.032 mg/kg; total dose, 0.063 mg/kg) and the reversal of the effect of apomorphine by LSD (0.05 and 0.1 mg/kg i.v.).

was a gradual process that required 25–30 min ($n = 3$) before baseline rates were restored.

All 7 cells suppressed by LSD had firing rates above 3.0 Hz (range: 3.0–7.0 Hz); in contrast, of the 6 cells that were not suppressed by LSD, only 2 had firing rates above 3.0 Hz. Fisher's exact test of significance for a $2 \times 2$ contingency table (Fisher, 1958) showed that the tendency for A10 DA cells to be suppressed by LSD was significantly related to baseline firing rate ($P < 0.05$).

To investigate the possibility that LSD might exert an antagonist effect on A10 DA cells, apomorphine was tested on those cells ($n = 6$) that were excited or were unresponsive to LSD (Fig. 3B). Following administration of LSD (mean dose: 0.425 mg/kg i.v.) the $ID_{50} \pm SEM$ for apomorphine-induced suppression of A10 DA cells ($0.037 \pm 0.004$ mg/kg) was significantly greater ($t(17) = 5.61$, $P < 0.01$) than that obtained from drug-free rats ($0.007 \pm 0.001$ mg/kg, Wang, 1981). In addition, LSD (0.15 mg/kg i.v.) reversed the rate-depressant effect of apomorphine ($n = 3$; Fig. 3B) but not that of lisuride ($n = 2$).

*Effects of 5-MeODMT on A10 DA cells*

To determine whether the effects of LSD and lisuride on A10 DA neurons might be mediated by their potent agonist actions on 5-HT receptors, a comparison was made of the effects of LSD and lisuride to those of 5-methoxy-*N*-*N*-dimethyltryptamine (5-MeODMT), a relatively selective agonist at the proposed 5-$HT_1$ binding site (Blackshear, Steranka and Sanders-Bush, 1981). Unlike LSD or lisuride, 5-MeODMT (0.05–0.75 mg/kg) potently increased the firing rate of 4 out of 5 A10 DA cells tested (Fig. 4A); the average increase was to 156% of baseline and the maximum increase was to 214% of baseline. In addition, 5-MeODMT accelerated the

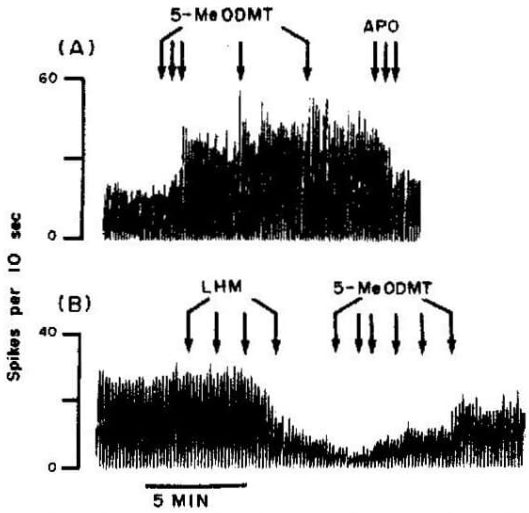


Fig. 4. Effects of 5-methoxydimethyltryptamine (5-MeODMT) on the firing rates of A10 dopamine (DA) neurons in the rat ventral tegmental area. (A) Typical increased firing rate of an A10 DA neuron produced by increasing intravenous doses of 5-MeODMT (0.05, 0.1, 0.2, 0.4 and 0.8 mg/kg; total dose, 1.55 mg/kg) on an A10 DA neuron and the return to baseline firing rate caused by apomorphine (APO; 0.001, 0.002 and 0.004 mg/kg i.v.). (B) Suppression of an A10 DA neuron by increasing intravenous doses of lisuride (0.001–0.008 mg/kg; total dose, 0.015 mg/kg) and the subsequent increased firing rate caused by 5-MeODMT (0.05–1.6 mg/kg; total dose, 3.15 mg/kg i.v.).

activity of 3 out of 4 A10 DA cells that had been suppressed by lisuride (Fig. 4B).

*Interaction between putative 5-HT antagonists and LSD, lisuride and 5-MeODMT*

To determine whether the effects of LSD, lisuride and 5-MeODMT on A10 DA cells might be mediated by different 5-HT receptors, the putative 5-HT antagonists ketanserin and metergoline were administered in combination with LSD, lisuride and 5-MeODMT. Ketanserin is reported to be a selective antagonist of the proposed 5-$HT_2$ binding site (Leysen, Awouters, Kennis, Laduron, Vandenbeck and Janssen, 1981), whereas metergoline has a similar high affinity for both the 5-$HT_1$ and 5-$HT_2$ bindings sites (Blackshear *et al.*, 1981; Leysen *et al.*, 1981). Ketanserin (0.05–2.0 mg/kg) was unable to prevent or reverse the effects of either LSD ($n = 6$), lisuride ($n = 10$) or 5-MeODMT ($n = 2$). In rats pretreated with metergoline, lisuride was either unable ($n = 2$) or only partially able ($n = 3$) to reduce the firing rate of A10 DA neurons whereas LSD produced no effects whatsoever ($n = 4$), even in cells with firing rates above 3.0 Hz. Metergoline failed to alter the rate-enhancing effects of 5-MeODMT ($n = 3$). Since metergoline also has a relatively high affinity for DA receptors (Leysen *et al.*, 1981), its ability to prevent the rate-depressant effects of apomorphine on A10 DA cells ($n = 3$) was also tested. Metergoline significantly ($t\,(14) = 5.58$, $P < 0.001$) increased the $ID_{50}$ for apomorphine ($0.074 \pm 0.01$ mg/kg) and prevented complete suppression of the firing of A10 DA cells even with large doses of apomorphine (> 1.0 mg/kg).

*Effects of lisuride, LSD and 5-MeODMT in rats with brain transections*

Cutting the ascending and descending projections (Fig. 5) to the ventral tegmental area at A 2.0 and A 5.5 failed to modify the characteristic effects of lisuride ($n = 6$), LSD ($n = 4$) or 5-MeODMT ($n = 3$) on A10 DA neurons. In acutely transected rats, the $ID_{50}$ for lisuride was $0.02 \pm 0.005$ mg/kg and the mean dose required for complete suppression of firing was $0.048 \pm 0.01$ mg/kg; neither of these results was significantly different from those obtained from rats without transections. In acutely transected rats, LSD partially suppressed the firing of 2 A10 DA cells (one to 50% and one to 80% of baseline firing rate), increased the firing rate of one cell (to 120% of baseline), and had no effect on one cell. 5-Methoxy-*N*-*N*-dimethyltryptamine increased the firing rates of all 3 cells tested in rats with acute transections; the average increase was to 142% of the baseline rate which did not differ significantly from results obtained from rats without transections.


Fig. 5. Saggital section of a rat brain illustrating a recording site (asterisk) of an A10 dopamine neuron in the ventral temental area approx. 0.5 mm lateral from the midline of a rat in which acute brain transections (arrows) had been made both anterior and posterior to the recording site. Abbreviations: FC, folia cerebelli; NRD nucleus raphe dorsalis; FR, fasciculus retroflexus; LM, lemniscus medialis; NR, nucleus ruber.

*Effects of lisuride and LSD on non-DA neurons in the ventral tegmental area*

Lisuride and LSD were also tested on neurons in the ventral tegmental area that did not display typical DA neuron characteristics (German *et al.*, 1980; Wang, 1981; Yim and Mogenson, 1980). Of the 5 non-DA cells tested with lisuride, 1 cell was suppressed to 15% of baseline by a total dose of 0.256 mg/kg, 2 cells were excited (> 200% of baseline) and 2 were unresponsive. Of the 4 non-DA cells tested with LSD, 2 cells were excited (> 160% of baseline) and 2 cells were not affected.

## DISCUSSION

These experiments have demonstrated that lisuride potently suppressed the firing rates of A10 DA cells, an effect that is characteristic of DA agonists (Bunney *et al.*, 1973; Wang, 1981), but failed to consistently alter the firing rates of non-DA neurons in the ventral tegmental area. The $ID_{50}$ for suppression of A10 DA cells by lisuride was similar to that reported for lisuride on A9 DA cells (Walters *et al.*, 1979a,b). As previously demonstrated on A9 DA cells (Walters *et al.*, 1979a,b), haloperidol was ineffective in reversing the suppression of firing induced by lisuride but was capable of preventing the effect, suggesting that lisuride acted as a non-competitive or irreversible DA agonist, as was recently demonstrated for another ergot derivative, bromocriptine (Bannon, Grace, Bunney and Roth, 1980; Marek and Roth, 1980). This interpretation is further supported by the fact that, following partial suppresssion of the activity of an A10 or A9 DA neuron by lisuride, apomorphine was unable to suppress further the firing rate of the cell. Unlike LSD (see below), lisuride did not exert a typical DA antagonist effect because lisuride failed to reverse the rate-depressant effects of apomorphine on A10 DA cells.

The mechanisms by which lisuride suppressed the activity of A10 DA neurons did not seem to involve forebrain feedback pathways because even a com-

plete forebrain transection failed to alter the rate-depressant effects of lisuride. This is in contrast to the effects of lisuride on A9 DA neurons because the rate-depressant effects of lisuride were significantly decreased when neurons in the caudate nucleus were destroyed with kainic acid to prevent feedback to A9 DA neurons via the striatonigral pathway (Walters *et al.*, 1979a). Whether this represents a true difference between A9 and A10 DA cells or might be due to different lesioning techniques (acute mechanical cuts vs chronic chemical lesions) is presently under investigation. Nevertheless, the results suggest that the potent rate-depressant effects of lisuride on A10 DA cells involve local mechanisms within the ventral temental area. To determine whether lisuride acted at somatodendritic DA autoreceptors will require additional experiments with microiontophoretic techniques.

In contrast to lisuride, LSD exerted mixed effects on A10 DA cells, partially suppressing the firing of some cells, accelerating the firing of some cells and exerting no effects on others. Previous studies of the effects of LSD on A9 DA cells have yielded conflicting results. Early investigations reported that LSD exerted no effects on the firing rates of A9 DA cells (Bunney *et al.*, 1973; Svensson, Bunney and Aghajanian, 1975). However, these reports failed to include complete dose-response analyses of the effects of LSD. More recently, Christoph *et al.* (1977) reported that LSD exerted mixed effects on A9 DA cells. However, unlike the findings of Christoph *et al.* (1977), the rate-depressant effects of LSD on A10 DA cells were neither abrupt nor transient. In this respect, the present results resemble more closely those of Walters *et al.*, (1979a,b) who reported a gradual partial rate-depressant effect of LSD on A9 DA cells. Interestingly, the present results suggested that A10 DA cells with firing rates above 3.0 Hz were more likely to be suppressed by LSD than A10 DA cells with firing rates below 3.0 Hz. Thus, the effects of LSD on A10 DA neurons were dependent upon the spontaneous activity of the cell being tested.

The partial suppression of A10 neuronal activity by LSD, which was reversed by haloperidol suggests that LSD is only a weak DA agonist *in vivo*, a conclusion that is supported by previous biochemical (Kehr and Speckenbach, 1978) and behavioral (Holohean *et al.*, 1982) studies. As previously demonstrated for A9 DA neurons (Christoph, Kuhn and Jacobs 1978), LSD also exerted an antagonist action on A10 DA neurons, reversing the rate-depressant effect of apomorphine. This reversal was not due to a 5-HT agonist action of LSD because, unlike 5-MeODMT (see below), LSD was not able to accelerate the activity of A10 DA cells suppressed by lisuride. In addition, when LSD was administered before apomorphine, the doses of apomorphine required to suppress A10 DA neurons were significantly greater than those required to suppress unit activity in drug-free rats. Thus, the present results are consistent with many previous reports that LSD is a weak DA agonist which also exerts partial DA antagonist-like actions (Christoph *et al.*, 1978; Creese, Burt and Snyder, 1975; Kehr and Speckenbach, 1978; Persson, 1977; VonHungen *et al.*, 1974; Walters *et al.*, 1979b). The DA-antagonist properties of LSD may also be responsible for the increased firing rate of some A10 DA cells seen following the administration of LSD because DA antagonists sometimes induce a slight acceleration of the firing of A10 DA cells (Fig. 2B). However, it is also possible that the LSD-induced acceleration was due to a 5-HT agonist action of LSD similar to that of 5-MeODMT.

Since the ventral tegmental area receives a relatively dense input form the dorsal raphe nucleus (Azmitia and Segal, 1978; Moore, Halaris and Jones, 1978; Phillipson, 1979; Simon, LeMoal and Calas, 1979), and since lisuride, LSD and 5-MeODMT exert potent rate-depressant effects on 5-HT neurons (Aghajanian and Vandermaelen, 1982; DeMontigney and Aghajanian, 1977; Rogawski and Aghajanian, 1979; Walters *et al.*, 1979b), it is possible that the effects of lisuride and LSD on A10 DA cells were mediated indirectly via 5-HT mechanisms. This possibility seems unlikely since lisuride, LSD and 5-MeODMT exerted markedly different effects on A10 DA neurons, i.e. lisuride exerted only rate-depressant effects, 5-MeODMT exerted only rate-enhancing effects and LSD exerted mixed effects. In addition, transections of the ascending and descending afferent pathways to the ventral tegmental area, which included the ascending 5-HT projections from the dorsal raphe nucleus, failed to modify the rate-depressant effect of lisuride or the mixed effects of LSD on A10 DA cells. The results obtained with 5-HT antagonists also failed to implicate a role for 5-HT receptors in the effects of lisuride and LSD. The 5-$HT_2$ antagonist ketanserin (Leysen *et al.*, 1981) failed to prevent or reverse the effects of lisuride or LSD; therefore, the proposed 5-$HT_2$ binding sites were probably not involved in the effects of these ergots on A10 DA cells. Metergoline, a 5-HT antagonist which displays comparable high affinities for both the 5-$HT_1$ and 5-$HT_2$ sites (Blackshear *et al.*, 1981; Leysen *et al.*, 1981), partially prevented the effects of lisuride and LSD. However, since metergoline also has a relatively high affinity for DA receptors (Leysen *et al.*, 1981), the effects of metergoline were probably due to antagonism of DA receptors. This is supported by the fact that metergoline also partially blocked the rate-depressant effects of apomorphine. Due to the lack of a specific antagonist of the 5-$HT_1$ site, a possible role of 5-$HT_1$ sites in the effects of LSD and lisuride on A10 DA neurons cannot be completely excluded; nevertheless, in view of other results (above), such a role seems unlikely.

It has been demonstrated (DeMontigney and Aghajanian, 1977; Haigler and Aghajanian, 1974) that small doses of LSD and 5-MeODMT exert a

preferential action on 5-HT autoreceptors located on 5-HT neurons in the dorsal raphe nucleus, suppressing their activity and thereby disinhibiting postsynaptic neurons in the amygdala and ventral lateral geniculate which receive a dense 5-HT input; in contrast, larger doses of LSD and 5-MeODMT suppress these postsynaptic neurons (De Montigney and Aghajanian, 1977; Haigler and Aghajanian, 1974). The doses of 5-MeODMT that increased the firing rates of A10 DA neurons act primarily on postsynaptic 5-HT receptors; therefore, it is unlikely that the excitant effect was due to disinhibition subsequent to suppression of serotonergic neurons in the dorsal raphe. This is supported by the finding that complete transections of fibres ascending to the ventral tegmental area failed to alter the excitant effects of 5-MeODMT. Interestingly, neither ketanserin nor metergoline altered the excitant effects of 5-MeODMT on A10 DA cells. The lack of antagonism by metergoline is particularly surprising since it has been reported that 5-MeODMT has a higher affinity for 5-$HT_1$ than 5-$HT_2$ binding sites (Blackshear *et al.*, 1981). Thus, it appears that the effects of 5-MeODMT on A10 DA neurons were mediated by receptors that do not correspond to either the 5-$HT_1$ or 5-$HT_2$ sub-types. The effects of 5-MeODMT also did not involve DA receptors since 5-MeODMT (unlike haloperidol) increased the firing rates of DA cells that had been suppressed by lisuride; therefore, 5-MeODMT was probably acting at receptors that were not occupied by lisuride. Clearly, additional studies are needed to elucidate the mechanisms by which 5-MeODMT increased A10 DA cell activity.

In conclusion, these results have demonstrated both qualitative and quantitative differences between the effects of LSD and lisuride on A10 DA neurons in the ventral tegmental area of the rat. The present findings are consistent with the view that lisuride is considerably more potent than LSD as a DA agonist *in vivo* (Holohean *et al.*, 1982, Horowski, 1978; Kehr and Speckenbach, 1978; Walters *et al.*, 1979a,b; White and Appel, 1982a,b). Since LSD is a potent hallucinogen whereas lisuride is not, the present evidence fails to support the hypothesis that a DA agonist action is intricately involved in the potency of hallucinogenic drugs (Christoph *et al.*, 1977; Jacobs *et al.*, 1977). In fact, the results suggest that the marked decrease in A10 DA neuronal activity caused by lisuride may contribute to its *lack* of hallucinogenic potential. Of course, the actions of these ergots at the target sites of A10 DA cells (e.g. the nucleus accumbens and frontal cortex) may also play an important role in their different subjective effects. In addition, since LSD and lisuride are equipotent at depressing 5-HT neuronal activity (Rogawski and Aghajanian, 1979; Walters *et al.*, 1979b), it seems increasingly likely that differences between the effects of LSD and lisuride on postsynaptic 5-HT receptors may play an important role in determining hallucinogenic potency (McCall and Aghajanian, 1980; Wang and Aghajanian, unpublished).

*Acknowledgements*—We thank Pam Dore for valuable technical assistance and Jan Heizer for preparing the manuscript. We also acknowledge the generous gifts of drugs by Farmitalia (metergoline), Janssen Pharmaceutica (ketanserin), McNeil Laboratories (haloperidol) and Schering AG (lisuride). This research was supported by USPHS Grant MH-34424 and a grant from the Scottish Rite Schizophrenia Research Program, NMJ, U.S.A. Rex Y. Wang is also a recipient of Research Scientist Development Award Type II MH 00378.

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