Lergotrile
Lisuride
LSD

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EFFECTS OF ERGOLINES ON DOPAMINERGIC AND SEROTONERGIC SINGLE UNIT ACTIVITY

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INTRODUCTION

Ergot derivatives have been used as therapeutic agents for a relatively long time (Dale, 1906). However, this class of drugs is obviously inducing renewed and growing interest among pharmacologists as unique derivatives are synthetized and new pharmacological uses become apparent. It appears that considerable research effort will be required to determine how major and minor variations in side chain and ring structure relate to the variety of effects these drugs produce. In the CNS, there is evidence (see this volume) that, as a group, the ergolines and ergopeptines can interact with (at least) three different transmitter systems, serotonin, dopamine, and norepinephrine, and potentially affect both pre- and postsynaptic receptors for these transmitters. The drugs have been most commonly thought to act as agonists, but are also described as partial agonists, indirect-acting agonists (inducing transmitter release), or as antagonists of these transmitters (Fuxe et al., 1977; Creese et al., 1975; U'Prichard et al., 1977). The most obvious explanation for the different spectrums of behavioral and neurochemical effects produced by the individual ergot derivatives is that each ergot derivative may interact at each of the different receptor sites in different ways and to differing extents. The challenge is to sort out these effects and to ascribe the various pharmacological advantages and disadvantages to specific or multiple sites and mechanisms of action.

Single unit recording investigations of effects of systemic administration of ergot derivatives on identified CNS neurons can contribute to this endeavor by bridging the gap between clinical and behavioral observations, and predictions about sites of action from in vivo and in vitro biochemical experiments. In the present study, we have focused on the effects of two of the newer ergolines on the activity of the dopamine containing cells in the substantia nigra pars compacta and the serotonergic cells of the dorsal raphe of the rat. Lergotrile mesylate (d-2-chloro-6-methylergoline-8β-acetonitrile methane sulfonate) and lisuride hydrogen maleate (N-[D-6-methyl-8-isoergolenyl]-N',N'-diethylcarbamide hydrogen maleate) were chosen because of their apparent, although somewhat complex, interactions with the serotonin and dopamine systems and their therapeutic potential as antiparkinsonian agents (Horowski & Wachtel, 1976; Kehr, 1977; Silbergeld & Pfeiffer, 1977; Fuxe et al., 1977; Kebabian et al., 1977; Teychenne et al., 1978; Silbergeld et al., this volume). We have compared these drugs with apomorphine, a direct-acting dopamine agonist, amphetamine, an indirect-acting agonist, and with LSD (d-lysergic acid diethylamide bitartrate), an ergot whose effects on the raphe cells have been well characterized (Aghajanian et al., 1968; Haigler & Aghajanian, 1974).

EFFECTS OF LISURIDE AND LERGOTRILE ON DOPAMINERGIC UNIT ACTIVITY

Comparison with Apomorphine, Amphetamine and LSD

Systemic administration of drugs believed to cause increased stimulation of dopamine receptors has been known to produce a profound and rapid decrease in the tonic firing rate of the substantia nigra dopamine neurons (Bunney et al., 1973a, 1973b, 1975; Walters et al., 1975). In order to compare the ergots with previously studied dopamine agonists, the effects of both large single i.p. doses and multiple i.v. injections were studied.

Single unit recording techniques. Previous studies utilizing a combination of fluorescent histochemistry, antidromic stimulation and extracellular single unit recording techniques have identified the electrophysiologic characteristics of the dopaminergic neurons in the pars compacta of the substantia nigra and serotonergic neurons of the dorsal raphe (Aghajanian et al., 1968, 1970; Bunney et al., 1973b; Haigler & Aghajanian, 1974; Guyenet & Aghajanian, 1977). The firing rates and the properties of the extracellular action potentials of these cells have been shown to be distinguishable from those of the cells in the surrounding regions. These attributes make it possible to tentatively identify the dopamine and serotonin-containing cells during the recording experiment. The techniques utilized for unit activity recordings with single-barrel glass micropipettes have been described previously (Bunney et al., 1973b; Walters et al., 1978). Chloral hydrate anesthetized rats were used for all studies and a single cell per animal was monitored. At the end of each experiment, the site of the electrode tip was marked by iontophoretic ejection of dye from the electrode, and the precise location of the recording site was determined after the brains were fixed, sectioned and mounted.

Effects of intravenous cumulative doses. In the first series of experiments, the drugs were administered i.v. as the activity of a single dopamine cell was monitored. Firing rate was averaged over six 10 sec intervals beginning 30 sec after drug administration, and expressed as a percent of the activity recorded during a 5 min baseline period. In these studies, complete inhibition was defined as cessation of activity for more than 1 min. Successive doses were injected at 2 min intervals in increasing increments, so that each dose doubled the previously administered cumulative dose (i.e., 0.2., 0.2, 0.4, 0.8 mg/kg, etc.). Although administering the drugs in this way made it possible to compare their potencies over a wide range of doses, it should be pointed out that the response curves are not necessarily the same as those which would have been obtained if each individual dose had been given to a separate group of rats. Changes in the sensitivity of the dopamine system induced by the earlier doses of the drug, or delayed responses resulting from formation of active metabolites or gradual penetration of the blood-brain barrier, if occurring, could contribute to the responses seen with the multiple injections.

Previous studies in which amphetamine was administered in this manner showed that dopaminergic activity was significantly inhibited at approximately 0.1 μmol/kg (0.4 mg/kg). Amphetamine generally produced complete inhibition by the time 0.8 μmol/kg had been administered (Bunney et al., 1975).

The effects of apomorphine administered in increasing doses is shown in Fig. 1. After delivery of .004 μmol/kg (1.25 μg/kg), the unit activity of approximately half of the cells studied was significantly decreased from that observed during the 5 min baseline period. The typical cell was inhibited to approximately 50% of its baseline rate by .032 μmol/kg, and ceased firing for at least 1 min after administration of .25 μmol/kg. It was possible to bring almost all dopamine cells to a complete stop for a short time with increasing doses of this agonist. The inhibition induced by systemic administration of amphetamine and apomorphine has been

shown to be readily reversible by administration of a dopamine receptor blocker such as haloperidol (Bunney et al., 1973a, 1973b).

I.v. administration of increasing doses of lergotrile (Walters et al., 1978) and lisuride also consistently produced a decrease in the activity of substantia nigra dopamine cells (Fig. 1, 2A,B & 3A). As can be seen in Fig. 1, the potency of lisuride was similar to that of apomorphine. The typical cell was significantly inhibited by a dose of .003 μmol/kg, (1.5 μg/kg) and its firing rate was reduced to 50% of baseline by .055 μmol/kg. However, more cells (30%) were resistant to complete inhibition after lisuride than after apomorphine. The effects of this ergot were also slightly different from those of apomorphine in that the cells responded more slowly to haloperidol after inhibition with lisuride (Fig. 2C). In some cases, haloperidol, administered i.v. in doses up to 3 mg/kg, did not appear to cause any reversal of the effects of lisuride within the time that reversal was normally seen after other agonists (Fig. 2A). Since several reports indicate that haloperidol pretreatment can block behavioral and biochemical effects of lisuride believed to be mediated through dopamine receptor stimulation (Horowski & Wachtel, 1976; Kehr, 1977; Pieri et al., 1978b), we tried administering haloperidol first and then examining the effects of lisuride. Under these conditions, haloperidol was consistently able to block the inhibitory effects of lisuride on dopamine cell activity.

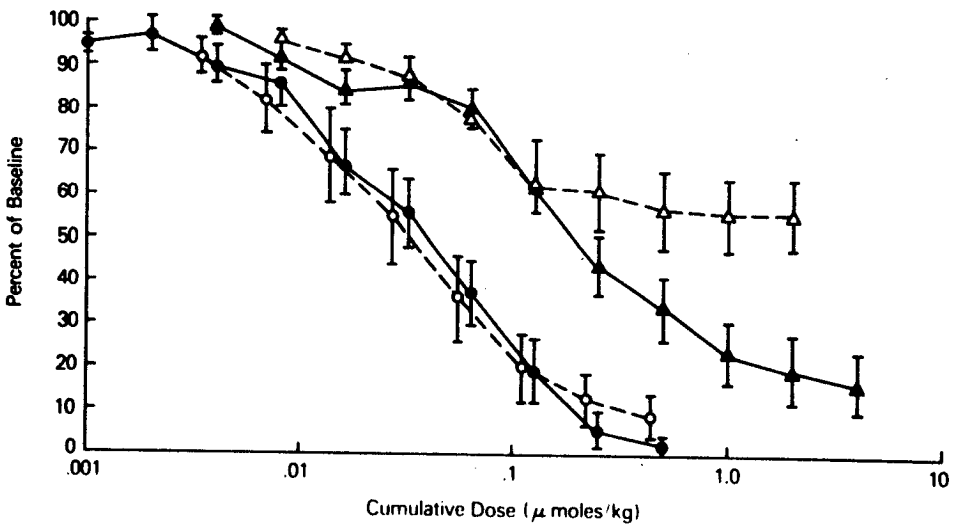

Fig. 1. Effects of apomorphine (●—●, N=9-11) and three ergoline derivatives, lisuride (○--○, N=9-13), lergotrile (▲—▲, N=11) and LSD (△--△, N=9-10) on the firing rates of dopamine cells in the substantia nigra pars compacta. The decreases in unit activity are expressed as percent of the baseline firing rate. Drugs were given in a series of increasing doses; each point represents the average response of several cells (one cell per rat) at that cumulative dose in the series. The bars indicate the standard error of the mean. The range in N reflects the fact that some cells were lost before the end of the entire series of injections and thus are not represented at the highest doses. Data for lergotrile and apomorphine taken in part from Walters et al. (1978).

Lergotrile was somewhat less potent than apomorphine and lisuride at inhibiting the activity of the substantia nigra dopamine cells (Figs. 1 and 3A). At least half of the cells studied were significantly affected by doses totaling .008 μmol/kg (3 μg/kg) and inhibited to 50% of baseline by .25 μmol/kg. Additional doses of lergotrile did depress unit activity further in many cases, but approximately 40% of the cells recorded became resistant to further inhibition after reaching 25 to 50% of the baseline rate. The effects of lergotrile were readily reversible by haloperidol (Walters et al., 1978).

The nondopaminergic cells in the pars reticulata of the substantia nigra have not been shown to be affected in any consistent dose-dependent way by administration of amphetamine or apomorphine (Bunney et al., 1973a, 1973b; Walters et al., 1975). Similarly, lergotrile (Walters et al., 1978) and lisuride did not consistently inhibit the firing of reticulata cells.

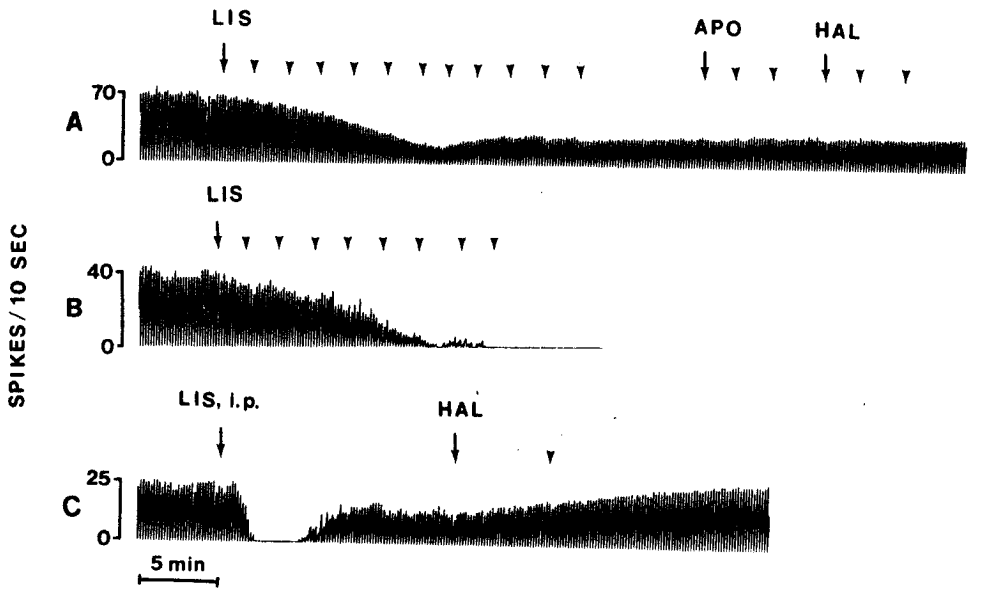

Fig. 2. Effect of lisuride (LIS) on the firing rate of dopamine cells in the substantia nigra pars compacta. A. Lisuride, administered i.v. as described in the text, in an increasing series of doses from .0015 mg/kg to a final cumulative dose of 3.2 mg/kg, resulted in partial inhibition of this cell. The cell reached maximum inhibition, 29% of baseline, at a cumulative dose of .1 mg/kg, and recovered to 46% of baseline despite additional lisuride injections. Apomorphine (APO, .5, .5, & 1.0 mg/kg i.v.) was unable to cause further inhibition. Haloperidol (HAL, 1, 1, & 1 mg/kg i.v.) did not reverse the inhibition; arrows indicate drug injections. B. I.v. administration of lisuride in a series from .0015 mg/kg to a final cumulative dose of .4 mg/kg produced total inhibition of firing of this cell. This response was more common than that shown in A. C. I.p. administration of lisuride (3.6 mg/kg) caused complete inhibition of firing of this cell for 2.8 min. The cell showed a typical biphasic recovery pattern, returning rapidly to a firing rate 64% of baseline after which recovery became very gradual. Haloperidol (1, 1 mg/kg i.v.) produced a gradual increase in the rate of recovery rather than the rapid reversal of the remaining inhibition seen commonly after other dopamine agonists.

LSD is an ergot derivative well known for its hallucinogenic effects in man and its striking ability to inhibit the activity of serotonergic neurons (Aghajanian et al., 1968; Haigler & Aghajanian, 1974). Recently, however, it has been suggested that this ergot may also have some direct effect on the dopamine system (Pieri et al., 1974; Da Prada et al., 1975; Burt et al., 1976). Christoph and coworkers (1977) have reported that LSD administered systemically can inhibit the activity of the nigral dopamine cells. In order to compare the effects of this hallucinogenic ergoline with those of lisuride and lergotrile, dopamine cells were monitored in the present study while LSD was administered in the same manner as the other agonists (Figs. 1 and 4B). Only slightly more LSD than lisuride or lergotrile was required to produce the initial significant inhibition of dopaminergic activity (.016 µmol/kg, 10 µg/kg). However, the maximum inhibition achieved by most cells as additional doses of LSD were administered averaged 53% of baseline and was less than that seen after the other ergolines. Only one cell out of 10 was brought to complete inhibition for a short period. Haloperidol reversed the effects of LSD.

Effects of larger doses. For many behavioral and biochemical studies, the ergots

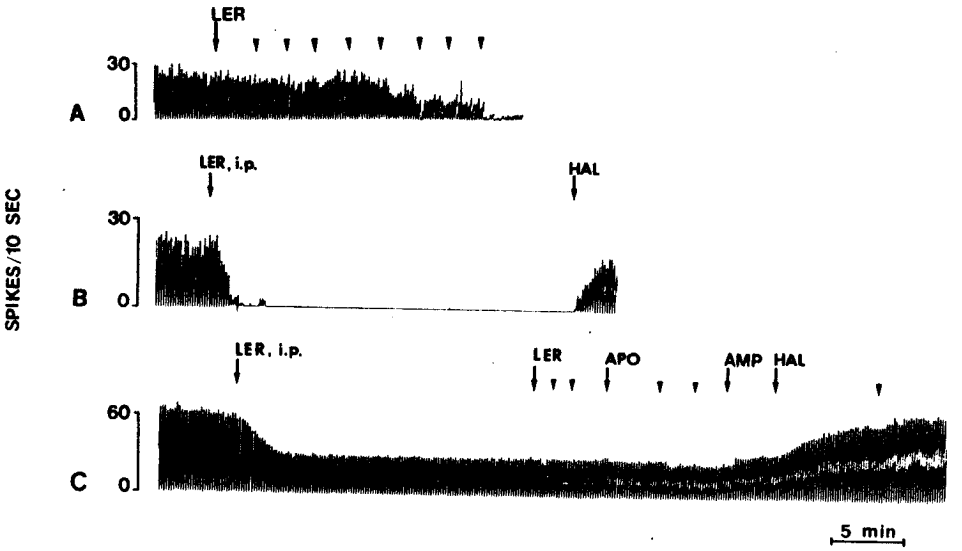

Fig. 3. Effect of lergotrile (LER) on the firing rates of dopamine neurons in the substantia nigra pars compacta. A. Lergotrile was administered i.v. as described in the text, in a series of increasing doses from .0015 mg/kg to a final cumulative dose of .4 mg/kg. At .4 mg/kg, the cell was markedly inhibited; arrows indicate drug injections. B. I.p. administration of 2.5 mg/kg lergotrile completely inhibited the activity of this cell. No recovery was seen until after administration of haloperidol (HAL, 1 mg/kg i.v.). Comparable responses were seen in about 40% of the cells recorded. C. I.p. administration of 2.5 mg/kg lergotrile produced a lasting partial inhibition of the firing of this cell, typical of that seen with remaining 60% of the units studied. The cell was relatively insensitive to further doses of lergotrile (.1, .2 & .4 mg/kg i.v.), to apomorphine (APO, .1, .2 & .4 mg/kg i.v.), and to amphetamine (AMP, 1 mg/kg i.v.). HAL (.1 & .2 mg/kg) reversed the inhibition. Data taken in part from Walters et al. (1978).

are injected i.p. in single doses larger than those studied in our multiple dose i.v. experiments. Thus, in a second series of studies, we also investigated dopaminergic activity during and after i.p. injections of 2.5 or 10 mg/kg lergotrile (Walters et al., 1978) and after 3.6 mg/kg of lisuride. Similar studies have previously been performed with apomorphine and with piribedil, a piperazine with dopamine agonist properties (Walters et al., 1975). In these earlier investigations, an interesting pattern of recovery was observed which was similar for both drugs. Within 1 to 2 min after i.p. injections of 2.0 mg/kg apomorphine, firing stopped abruptly and generally remained totally inhibited in these cells for a period averaging 7 min. This period was not substantially prolonged by increasing the amount of apomorphine injected. When firing resumed, recovery was biphasic (Bunney et al., 1973a; Walters et al., 1975). Activity returned rapidly to about 40% of baseline and then recovered more gradually.

After administration of a comparable molar dose of lergotrile, a somewhat different pattern of inhibition and recovery was seen (Figs. 3B,C) (Walters et al., 1977). Activity decreased to a point of either partial or complete inhibition. The average firing rate after 20 min was reduced to approximately 25% of baseline. Those cells which stopped completely showed no signs of spontaneous recovery for up to 20 min; at this time haloperidol was generally administered to reactivate the cell and determine that the electrode was still in the appropriate area. The activity of those cells (60%) which were not completely inhibited after lergotrile leveled off between 50 and 80% of the baseline rate; recovery was slow. One cell which was monitored for 55 min showed only 16% recovery. I.P. administration of 10 mg/kg lergotrile did not produce significantly greater inhibition of dopaminergic unit activity than did 2.5 mg/kg (Walters et al., 1978).

The effects of i.p. administration of lisuride were intermediate between those seen with apomorphine and lergotrile (Fig. 2C). A portion of the cells (45%) were completely inhibited initially and then after about 4 min, recovered in a biphasic manner similar to that seen after apomorphine. The cells which were only partially inhibited also showed a biphasic recovery after reaching their maximum point of inhibition. At 20 min, the average firing rate was 60% of baseline (N=9).

Assuming that the neurons recorded in these studies are representative of the substantia nigra dopamine cell population, these results suggest that the average firing rate of this population is more depressed 20-30 min after lergotrile administration than after lisuride, while apomorphine produces an intermediate effect. In addition, the individual dopamine cells in animals treated with apomorphine or lisuride are, after 20 min, generally active and in their slow second phase of recovery, while some cells in animals treated with lergotrile are still completely inhibited. Thus, although lisuride appears a more potent dopamine agonist than lergotrile when initial responses to small doses are considered, its inhibitory effects on dopaminergic activity appear to wear off more rapidly.

The responses of the dopamine cells to additional injections of agonists during the recovery period were also studied. These will be discussed below.

Possible Sites of Action

The ability of lergotrile and lisuride to produce a rapid, dose-dependent and haloperidol blockable attenuation of dopaminergic unit activity, comparable to that observed with apomorphine, is consistent with behavioral studies and biochemical observations, suggesting that these drugs may be acting, at least in part, as dopamine agonists (Clemens et al., 1975; Horowski & Wachtel, 1976; Fuxe et al., 1977; Kehr, 1977; Tye et al., 1977; Silbergeld & Pfeiffer, 1977; Horowski et al., 1978; Pieri et al., 1978a, 1978b). However, recent reports indicate that many of the ergot alkaloids cause either very little or no significant stimulation of

dopamine sensitive adenylate cyclase from striatal homogenates (Kebabian et al., 1977; Kebabian, this volume; Fuxe et al., 1977; Schmidt & Hill, 1977). This has provoked considerable confusion about the mechanism of action of these drugs and the relationship between dopamine receptors and dopamine sensitive adenylate cyclase.

One hypothesis which has been proposed to account for the inability of the ergots to stimulate striatal adenylate cyclase suggests that the drugs themselves may not be the active agents. However, although metabolites may play a significant role in mediating the effects of the slowly acting ergot, bromocriptine (Johnson et al., 1976), the potency of the two ergolines studied here and the rapid decrease in neuronal activity observed after i.v. or i.p. injection suggests that these drugs act directly and do not require metabolism to more active forms.

Another possible explanation is that these agents might be acting indirectly to stimulate dopamine receptors by promoting the release of dopamine. In fact, lergotrile has been shown to increase dopamine release in vitro from minces of forebrain tissue (Silbergeld & Pfeiffer, 1977; Silbergeld et al., this volume). To explore this issue, we investigated the effects of lergotrile on dopaminergic activity in rats pretreated with α-methylparatyrosine (AMPT) and reserpine (Walters et al., 1977, 1978). Inhibition of dopamine synthesis and storage by pretreatment with these agents completely blocks the ability of amphetamine to inhibit dopaminergic activity. Apomorphine's effects, on the other hand, are either unchanged or slightly increased. Lergotrile administered to animals pretreated with AMPT and reserpine still effectively inhibited the activity of substantia nigra dopamine neurons. With some of the intermediate doses tested, a slight attenuation in response to lergotrile was seen in the pretreated rats. The significance of this small attenuation is not clear. The fact that lergotrile still effectively depressed dopaminergic activity in the pretreated rats, and the relative potency of this ergot clearly distinguish it, in terms of its effects on dopaminergic unit activity, from drugs like amphetamine which act by increasing the release of dopamine rather than by mimicking dopamine at dopamine receptors.

The possibility that the changes in dopaminergic activity seen with administration of lergotrile and lisuride could be due solely to interactions of these drugs with the serotonergic and noradrenergic systems also seem unlikely. Several drugs which markedly affect the activity of the norepinephrine-containing neurons in the locus coeruleus, such as clonidine and the tricyclic antidepressants, have no significant effect on the activity of the dopamine neurons (Svensson et al., 1975; Nybäck et al., 1975). In addition, it does not appear that the ergots are altering dopaminergic activity by direct stimulation of serotonin receptors on dopamine neurons since iontophoresis of serotonin directly onto the dopamine cell bodies does not inhibit their firing (Aghajanian & Bunney, 1974). While indirect effects mediated through the serotonergic systems are more difficult to rule out, results presented here (see below) and other investigations (Pieri et al., 1974; Burt et al., 1976; Horowski & Wachtel, 1976; Christoph et al., 1977; Kehr, 1977) have not shown a close correlation between the relative effects of the ergolines on dopamine and serotonin-linked phenomena.

The question of whether the ergolines are directly active dopamine agonists could be most effectively resolved by iontophoretic studies combined with intracellular recordings. However, since several lines of evidence, including neuroendocrine, behavioral, receptor binding and neurophysiological studies, support the idea that the ergolines are dopamine agonists, it would appear that the ability of a drug to stimulate dopamine sensitive adenylate cyclase is not a reliable index of dopaminetic activity (Kebabian et al., 1978).

Net Effects on Dopamine-mediated Neurotransmission

If lergotrile and lisuride are acting, at least in part, as dopamine agonists, what do the changes in firing rates of the dopamine neurons indicate about the drugs' net effects on cells postsynaptic to the dopamine neurons? When it was initially observed that marked changes in firing rates of dopamine neurons could be induced by systemic administration of dopamine agonists, it was believed that these changes reflected the interaction of the drugs with striatal neurons innervated by the nigrostriatal dopamine system (Bunney et al., 1973a, 1973b). A striatonigral feedback loop was thought to modify the activity of the dopamine neurons in a way which would tend to compensate for the drug-induced changes in postsynaptic dopamine receptor stimulation (Carlsson & Lindqvist, 1963). Thus, the firing rate of the dopamine neurons would actually reflect the kind of balance struck between transmitter and drug on the postsynaptic side of the dopamine synapse. It has since been shown, however, that dopamine or apomorphine iontophoresed into the vicinity of a dopamine cell body can directly inhibit the activity of the dopamine neurons, presumably by interacting with dopamine receptors on the cell surface (autoreceptors) (Aghajanian & Bunney, 1977). This indicated that changes in dopaminergic firing rates induced by systemic administration of a dopamine agonist could be due, at least in part, to direct interactions of the drug with the autoreceptors. In addition, the observation that dopamine dendrites may contain releasable dopamine (Björklund & Lindvall, 1975) has suggested that the effects of amphetamine on dopaminergic activity may also be independent of a striatonigral feedback loop. Dendritic dopamine released by amphetamine could stimulate the autoreceptors on the dopamine neurons (Geffen et al., 1976; Paden et al., 1976).

More recently, it has been shown that dopamine neurons in rats with unilateral kainic-acid lesions of the striatonigral pathway show the same response to systemic apomorphine as do cells in control animals (Baring et al., 1978). Preliminary studies indicate that lisuride is also able to effectively inhibit dopaminergic activity in rats whose striatal neurons have been extensively destroyed by kainic-acid injections. Thus, it appears that changes in firing rates of dopamine neurons after systemic administration of dopamine agonists are not solely determined by the behavior of the postsynaptic cells.

Moreover, the presynaptic changes may not necessarily parallel postsynaptic changes. Aghajanian and coworkers have shown that receptors on the serotonin cell bodies are more sensitive to the effects of LSD than are the serotonin receptors on cells postsynaptic to the serotonin neurons (Haigler & Aghajanian, 1974). These studies indicate that characterization of the net effects of transmitter agonists in the CNS will require investigation of the effects of drugs on both the neurons utilizing the mimicked transmitter (presynaptic effects) and those innervated by that transmitter system (postsynaptic effects). As appears to be the case with LSD, it seems quite possible that monoamine agonists could preferentially affect the presynaptic autoreceptors of the neuron whose transmitter the agonist is mimicking, decreasing (if the transmitter is inhibitory) rather than increasing the amount of stimulation delivered to the postsynaptic receptors. It has been proposed that such an effect may account for some of the "antagonistic" actions of the dopamine agonists (Carlsson, 1975). While the results of the present study support the idea that lisuride and lergotrile can act as dopamine agonists, iontophoretic and systemic effects of these drugs at both pre- and postsynaptic sites will need to be investigated before the behavioral effects of these drugs can be effectively correlated with their actions on individual transmitter systems.

Agonist, Partial Agonist or Antagonist?

The effects of apomorphine and the ergolines on dopamine or haloperidol binding,

dopamine sensitive adenylate cyclase, and other biochemical and behavioral phenomena have lead many investigators to suggest that these agents are not "pure" agonists, but rather partial agonists or mixed agonist-antagonists (Bieger et al., 1972; Miller et al., 1974; Creese et al., 1975; Fuxe et al., 1977; Pieri et al., 1978a). Their different affinities for dopamine and haloperidol binding sites and their tendency to produce a dopamimetic effect in some systems at the same time that they block more potent effects of dopamine itself have contributed to the "partial agonist" concept. During previous studies with apomorphine and piribedil, some observations were made which appeared to bear a possible relationship to these phenomena (Walters et al., 1975). A firing resumed after a period of complete inhibition induced by either one of these agonists, the cells became, with additional injections of either agonist, totally resistant to any further inhibition. This suggested that the agonists were inducing some form of desensitization or change of the dopamine receptor population. In addition, once resistant to the agonist administered originally, the cells were also resistant to inhibition by the other agonist, or by amphetamine or L-dopa, suggesting that the effects of amphetamine and L-dopa were mediated through the same receptors as the agonists.

We investigated this phenomenon with the ergolines by administering apomorphine or amphetamine while dopamine cells were recovering from inhibition by lergotrile or lisuride. Pretreatment with either agent rendered the cells resistant to the effects of apomorphine or amphetamine, but lergotrile's ability to block was weaker than that of lisuride (Fig. 2A and 3C). LSD was the least effective at blocking the effects of apomorphine or amphetamine (Fig. 4C). Thus, there appeared a correlation between the ability of these putative dopamine agonists to initially depress the activity of the dopamine cells and their ability to subsequently block the effects of other direct and indirect acting dopamimetic drugs.

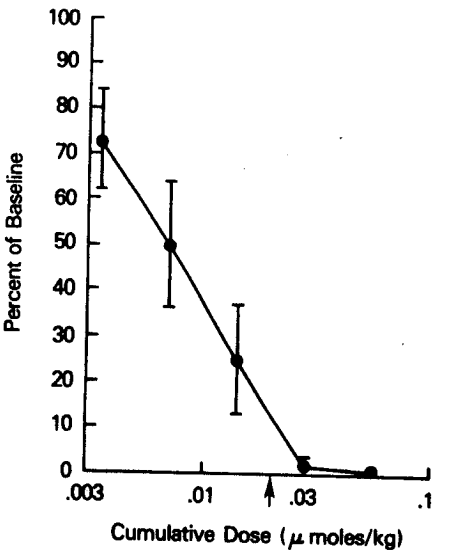

Fig. 4. Effects of lisuride (N=7) on the firing rates of serotonin neurons in the dorsal raphe. The decreases in unit activity are expressed as percent of the baseline firing rate. Lisuride was given in a series of increasing doses; each point represents the average response of several cells to that cumulative dose in the series. The bars indicate the standard error of the mean. The arrow indicates the average dose of LSD which causes 100% inhibition of the serotonin cells (Aghajanian et al., 1970; Haigler & Aghajanian, 1974).

These results do not agree with the suggestion, derived from some biochemical studies, that LSD is a better dopamine antagonist than lisuride (Kehr & Speckenback, 1978).

EFFECTS ON SEROTONERGIC UNIT ACTIVITY

Several studies have suggested that lisuride is a potent serotonin agonist as well as a dopamine agonist (Kehr, 1977; Da Prada et al., 1977; Pieri et al., 1978a, 1978b; Silbergeld, this volume). Consequently, we have compared the ability of this drug to inhibit the activity of serotonin-containing neurons in the dorsal raphe (Figs. 4C and 5) with that of LSD, a well established serotonin agonist. The average dose of systemic LSD required to completely inhibit activity of the

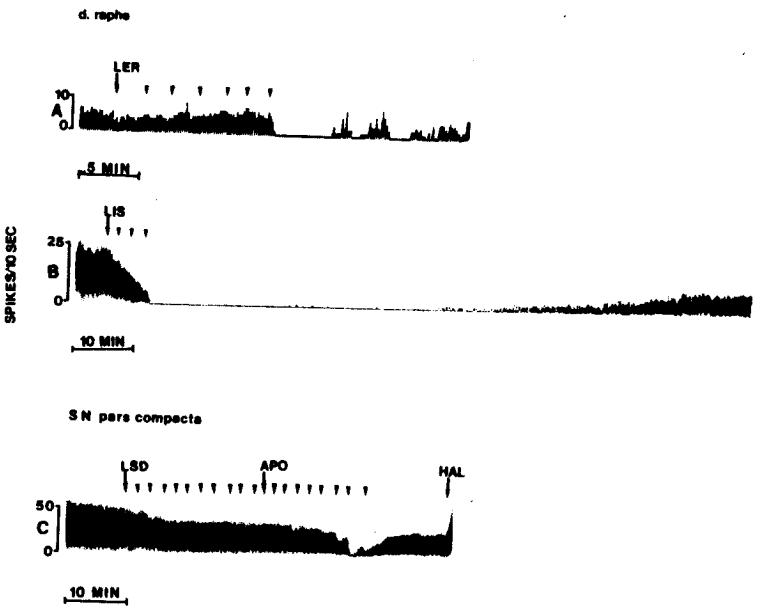

Fig. 5. A. The effect of lergotrile (LER) on the firing rate of a serotonin cell in the dorsal raphe. A series of increasing doses of lergotrile were administered i.v. from 1.5 µg/kg to a cumulative dose of .1 mg/kg. No inhibition of unit activity was seen until the final dose was given. Serotonergic activity was typically unaffected by low doses of lergotrile. Arrows indicate drug injections. B. The effect of i.v. lisuride (LIS) on the firing rate of a serotonin cell in the dorsal raphe. A series of increasing i.v. injections (1.5, 1.5, 3.1 & 6.2 µg/kg) resulted in a complete inhibition of this cell. A gradual spontaneous recovery began after 20 min. C. The effect of i.v. LSD on the firing rate of a substantia nigra pars compacta dopamine cell. A series of increasing doses from 5 µg/kg to the final cumulative dose of 5 mg/kg was given; the maximum inhibition, 71% of baseline, occurred with a cumulative dose of 80 µg/kg and firing remained at that rate despite subsequent LSD injections. Apomorphine (APO) was given i.v. in doses from .01 mg/kg to a cumulative dose of 2.5 mg/kg; although doses of apomorphine which, when given alone, would normally have caused inhibition, failed to have any effect on this cell. Larger doses did cause considerable depression of activity. Haloperidol (HAL, .5 mg/kg) reversed the inhibition.

dorsal raphe neurons is approximately .02 µmol/kg (12 mg/kg) (Aghajanian et al., 1970; Haigler & Aghajanian, 1974). The length of time the cells are completely inhibited by LSD appears dose-dependent (Aghajanian et al., 1968); recovery, unlike that seen in the dopamine system after administration of many of the dopamine agonists, is gradual. On a molar basis, lisuride, administered in a series of i.v. injections, as described above, appeared to have a potency similar to LSD (Fig. 4). After a dose of .03 µmol/kg, the activity of the raphe cells was inhibited by an average of 98%. Although this observation supports the idea that lisuride is a potent serotonin agonist, the possibility that these effects are due to interaction of lisuride with some other neurotransmitter system cannot be ruled out. Svensson and coworkers (1975) have shown that agents which inhibit the activity of norepinephrine neurons can indirectly affect the activity of the serotonin system. The potent effects of lisuride on serotonergic activity are interesting in view of the apparent lack of any indication in the clinical literature that lisuride is a hallucinogen like LSD (Herrman et al., 1977; Horowski et al., 1978). Preliminary studies with lergotrile indicate that this ergot derivative is less effective than lisuride or LSD at inhibiting the activity of the serotonergic neurons (Fig. 5A).

CORRELATIONS WITH BEHAVIORAL, BIOCHEMICAL, AND CLINICAL OBSERVATIONS

The present studies show that two synthetic ergoline derivatives, lergotrile and lisuride have inhibitory effects on the activity of the substantia nigra dopamine neurons. These results are consistent with the idea that lergotrile and lisuride are centrally acting dopamine agonists, and they correlate well with many observations from animal studies. The lowest doses found to cause significant decreases in dopaminergic activity in the present investigations are within the range of those doses which are minimally effective in inducing changes in prolactin levels in rats (Clemens et al., 1975; Graf et al., 1976). When doses producing 50% inhibition of dopaminergic activity are compared, lisuride's potency appears similar to that of apomorphine while lergotrile is less potent. These results correlate with the relative potencies of the ergolines at displacing haloperidol binding in striatal homogenates (Goldstein et al., 1977; Silbergeld et al., this volume). Comparison of the maximal decreases in dopaminergic activity induced by larger doses of these drugs 20 to 30 min after drug administration, shows that dopaminergic activity recovers somewhat faster after lisuride than after apomorphine while recovery after lergotrile is slower. Similarly, duration of stereotypy has been reported to be more prolonged after lergotrile than apomorphine (Silbergeld & Pfeiffer, 1977). LSD, found to be less effective at inhibiting dopaminergic activity than lisuride and the other agonists, is also less effective in inducing rotation in animals with 6-hydroxydopamine-induced lesions of nigrostriatal neurons (Pieri et al., 1978b).

On the other hand, these results do not correlate with the effects of the agonists on dopamine sensitive adenylate cyclase, as discussed above. It is also not obvious how they relate to the reported effects of the ergolines on in vivo dopamine synthesis. In the latter studies, the rate of striatal dopamine synthesis is estimated by measuring the accumulation of dopa after inhibition of dopa decarboxylase. Apomorphine produces a significant decrease in dopa accumulation with doses greater than 16 µg/kg. As larger doses are given, the effect of apomorphine levels off until a further inhibition is observed with doses greater than .5 mg/kg (Carlsson et al., 1977). After lisuride, dopa accumulation in the striatum is decreased at 30 and 100 mg/kg and returns toward control levels with doses of .3 and 1 mg/kg (Kehr, 1977). We found no significant change in dopa

accumulation with doses of lergotrile ranging from .1 to 10 mg/kg, although lergotrile did effectively reverse the increase in dopamine synthesis induced by inhibition of dopaminergic impulse flow with gamma-butyrolactone (Walters et al., 1978). LSD has been shown to increase dopa accumulation at doses of .125 to .5 mg/kg (Persson, 1977). Although it is not obvious why administration of LSD, lergotrile, and the higher doses of lisuride do not depress dopamine synthesis, the agents which do induce at least some attenuation of dopa accumulation, apomorphine and lisuride, were the most potent drugs in depressing dopaminergic activity. However, with single unit recording information on only the initial effects of low doses of the ergolines and no data on the rate of recovery from these doses, we are not able to make a really meaningful comparison. In addition, it should be pointed out that the changes in dopamine synthesis induced by drugs which both decrease dopaminergic activity and stimulate presynaptic dopamine receptors may reflect a complex balance between the tendency for dopamine synthesis to increase when firing is inhibited in these neurons, the counteracting effect of dopamine presynaptic-receptor stimulation on the phenomena and the potentiating effect of dopamine receptor blockade (Walters & Roth, 1976). Direct effects of the agonists on tyrosine hydroxylase may also complicate the picture, especially when they are given in large doses. These considerations illustrate the difficulty of inferring from changes in dopamine synthesis how drugs are affecting dopaminergic activity.

When the effects of the ergolines on dopamine and serotonin neurons are compared, it appears that lisuride has a more potent effect on serotonin neurons than on dopamine neurons, while lergotrile is less potent on the serotonin neurons than on the dopamine neurons. These observations agree with the findings that serotonin-mediated behavioral changes appear to dominate when lisuride is administered to rats (Silbergeld et al., this volume; Da Prada et al., 1977). However, until the relative effects of the ergots at postsynaptic dopamine and serotonin receptors, as well as at pre- and postsynaptic noradrenergic receptors, are known, it is difficult to assign specific behavioral effects of these drugs to the different transmitter systems. The obvious question emerging from the similarity between LSD and lisuride's effects on raphe cell activity is why lisuride is not reported to produce hallucinations in man (Herrmann et al., 1977; Horowski et al., 1978). Perhaps lisuride is relatively more potent than LSD at postsynaptic serotonin receptors, in which case its ability to inhibit the serotonin neurons is counterbalanced by postsynaptic receptor stimulation. Alternatively, a difference in the interactions of lisuride and LSD with nonserotonergic systems, in particular, the more potent effect of lisuride on the dopamine system, might somehow account for the different psychotomimetic effects of the two drugs.

Finally, the present results are consistent with the idea that lergotrile and lisuride are centrally acting dopamine agonists in man, potentially effective in the treatment of parkinsonian and hyperprolactinemic states (Calne, this volume; Lemberger et al., 1974; Horowski et al., 1978; Teychenne et al., 1978). These studies may also have some bearing on the apparently paradoxical ability of some dopamine agonists to reduce the symptoms of Huntington's chorea (Corsini et al., 1978; Tamminga, this volume). Such an effect is generally associated with dopamine antagonism rather than agonism. However, it appears that there may be several ways the dopamine agonists could partially diminish or limit dopamine's effects at the postsynaptic receptor. They might preferentially stimulate autoreceptors on dopamine cells, inhibiting dopamine neurons at lower doses than those which could stimulate the postsynaptic dopamine receptors (Carlsson, 1975). In addition, if the agonist-induced resistance to effects of other agonists or amphetamine observed in these studies is reflected in a similar change at postsynaptic receptor sites, agonists may not only be self-limiting in their postsynaptic effects, but may also limit the effects of endogenous dopamine.

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