European Journal of Pharmacology, 81 (1982) 595–602



# DOPAMINERGIC AND SEROTONERGIC MEDIATION OF THE DISCRIMINABLE EFFECTS OF ERGOT ALKALOIDS

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Received 30 March 1982, accepted 3 May 1982

A.M. HOLOHEAN, F.J. WHITE and J.B. APPEL, *Dopaminergic and serotonergic mediation of the discriminable effects of ergot alkaloids*, European J. Pharmacol. 81 (1982) 595–602.

The involvement of dopamine (DA) and serotonin (5-HT) neuronal systems in the discriminative stimulus effects of various ergot derivatives was assessed by administering four ergots to 36 rats which had been trained to discriminate either apomorphine (APO) or d-lysergic acid diethylamide (LSD) from saline. Lergotrile, lisuride and LSD substituted for APO (0.25 mg/kg) while bromocriptine and ergonovine (ergometrine) did not; only lisuride mimicked LSD (0.08 mg/kg). Antagonism tests showed that the DA antagonist haloperidol but not the 5-HT antagonist BC-105 (pizotifen) blocked the APO cue; both the LSD cue and the substitution of LSD for APO were blocked by BC-105 but not by haloperidol. It was concluded that DA receptor activation plays a prominent role in the discriminative stimulus effects of lergotrile and lisuride as well as APO and a secondary role in the LSD cue; 5-HT seems to be of major importance in the mediation of the effects of LSD and, to a lesser extent, lisuride. The functions of the two monoamines in the discriminable effects of bromocriptine and, particularly, ergonovine are less clear.

Apomorphine  Drug discrimination  LSD  Dopamine  Serotonin  Ergot alkaloids

## 1. Introduction

Ergot alkaloids have recently been the focus of considerable interest and new derivatives with important pharmacological actions and clinical applicability have been synthesized (Berde and Schild, 1978; Fuxe and Calne, 1979; Goldstein et al., 1980). These compounds can act at peripheral and central serotonin (5-hydroxytryptamine; 5-HT), dopamine (DA) and norepinephrine (NE) receptors either as agonists, antagonists or mixed agonist-antagonists (Berde, 1980).

Although one ergot, d-lysergic acid diethylamide (LSD), is best known for its hallucinogenic properties (Hoffman, 1959), many structurally related compounds have been used clinically for decades (Dale, 1906). For example, because of its vasoconstrictive ability ergonovine (ergometrine) is effective in blocking post-partum hemorrhage (Kharasch et al., 1936) and is used as a diagnostic test for variant angina (Brazenor and Angus, 1981). Ergotamine, lisuride and methysergide exert peripheral anti-5-HT effects and therefore have been used as migraine prophylactics (Lance et al., 1970; Somerville and Herrmann, 1978). Bromocriptine, lergotrile and lisuride have therapeutic activity in disorders involving reduced stimulation of DA receptors such as acromegaly, hyperprolactinemia and Parkinson's disease (Calne, 1978; Fluckiger, 1980; Lemberger, 1978).

Ergot derivatives also elicit diverse effects in animals which are thought to reflect the different neuronal systems with which they interact; thus, behaviors said to indicate either DA (locomotor activity, stereotypy and rotational behavior) or 5-HT ('serotonin syndrome') stimulation have been

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observed following several ergolines (Fuxe et al., 1978; Ögren et al., 1979; Silbergeld et al., 1979). While these behaviors often can contribute valuable information regarding neuronal mechanisms, they are sometimes difficult to interpret. For example, (1) although locomotor activity following DA agonists appears to be mediated primarily by mesolimbic DA receptors, locomotor activity in general may be modulated by neuronal systems containing 5-HT, γ-aminobutyric acid (GABA) or acetylcholine (ACh) (Kelley, 1977). (2) Stereotypy induced by DA agonists is a complex syndrome which is thought to be mediated by the nigrostriatal DA system but is also influenced by 5-HT (Costall and Naylor, 1976) and ACh (Scheel-Krüger, 1970) mechanisms. (3) While rotational behavior in rats with unilateral 6-hydroxydopamine-induced lesions of nigrostriatal DA fibers is influenced by dopaminergic drugs such as DA and apomorphine and is thought to be due to supersensitivity of denervated DA receptors, both 5-HT and NE can also induce contralateral rotation in lesioned animals (Costall et al., 1976). (4) The 'serotonin syndrome' consists of a set of stereotyped behaviors which can be differentiated from those induced by DA agonists and, as the name implies, is thought to reflect specifically 5-HT activation (Jacobs, 1976; Sloviter et al., 1978); however, this syndrome can be influenced by DA activity (Silbergeld and Hruska, 1979; Sloviter et al., 1978) and intracerebral injection of 5-HT does not always cause the 'syndrome' (Pfister et al., 1978). In view of these problems, it may not be wise to attribute particular neuronal sites of action to a compound solely because it elicits any or all of these behaviors, particularly when the agent in question has as many diverse effects as ergots.

One behavioral assay of in vivo neuropharmacological activity that is less encumbered by problems of lack of sensitivity and specificity is drug discrimination (Colpaert and Rosecrans, 1978). In this procedure, an organism must respond to internal changes ('states') produced by a drug in order to obtain reinforcement. The drug discrimination (DD) technique is advantageous because it is reliable (over time), robust (discriminations are extremely accurate), sensitive (to very low doses) and specific to particular neuronal systems (Rosecrans and Glennon, 1979). Unlike any other pharmacological procedure (including those discussed above) DD has successfully differentiated the relative roles of 5-HT and DA in the actions of LSD and lisuride (White and Appel, 1982a).

In the present study, DD procedures were used to analyze the roles of DA and 5-HT in mediating the behavioral effects of four ergot derivatives: bromocriptine, ergonovine, lergotrile and lisuride. Separate groups of rats were trained to discriminate either 0.25 mg/kg of apomorphine (APO) or 0.08 mg/kg of LSD from saline. APO was chosen because its discriminable properties are known to be mediated specifically by its agonistic action at central DA receptors (Colpaert et al., 1975, 1976); LSD was used because of its structural similarity to other ergots and because its discriminable effects are mediated by its agonistic action at central 5-HT receptors (Kuhn et al., 1978; Rosecrans and Glennon, 1979; White and Appel, 1982c). Once accurate discriminations were evident and the specificity of each training drug cue was demonstrated by dose-response and antagonism tests, the ergot derivatives were administered to each group in substitution tests to ascertain the degree of DA and 5-HT involvement in their actions.

The findings confirm the fact that ergoline derivatives produce behavioral effects which are mediated by DA and 5-HT receptors. Specifically, lergotrile and lisuride produce discriminable effects that are qualitatively similar to APO. LSD also produces an APO-like stimulus although this effect is partial and dependent upon 5-HT receptor activation. In addition to acting as a DA agonist, lisuride also acts as a 5-HT agonist and mimics the discriminative stimulus (DS) effect of LSD. The DS effects of bromocriptine and ergonovine do not closely resemble either APO or LSD although further investigation seems warranted.

## 2. Materials and methods

### *2.1. Subjects*

Thirty-six experimentally naive, male, albino, Sprague-Dawley rats, weighing 250–350 g were

used. They were housed individually in stainless steel cages located in a room maintained under constant temperature (21–23°C), humidity (40–50%) and light-cycle (07:00–19:00 h light). Lab chow was available ad libitum; access to water was restricted to 48 h prior to the start of the experiment. Animals were maintained at 80% of their free-feeding weights thereafter by restricting water intake.

### 2.2. Apparatus

Eight two-lever operant chambers (BRS/LVE Model 143-25), housed in sound- and light-attenuating shells (BRS/LVE Model 132-04), were used. Located on one wall of each chamber were two response levers separated equidistantly by a dipper which delivered 0.1 ml of water. Illumination was provided by a 28 V white house light; ventilation and masking noise were supplied by an exhaust fan. Electromechanical and solid state programming and recording equipment were located in an adjoining room.

### 2.3. Training procedure

Drug discrimination training procedures have been described in detail elsewhere (White and Appel, 1981). Twelve rats were trained to discriminate 0.25 mg/kg APO from saline; 24 rats were trained to discriminate 0.08 mg/kg of LSD. During each training session animals were given an intraperitoneal (i.p.) injection of either a drug or saline prior to being placed into the chamber; a 30 min injection-test interval was used in the APO group and a 15 min interval in the LSD group. Training began on a schedule of continous water reinforcement (FR 1) with only one (stimulus-appropriate) lever present. All animals received saline on the first day of training; thereafter, the order of drug administration was random with the restriction that no condition be present for more than three consecutive days. To control for position preference, one-half of the animals in each group were reinforced following right-lever choice in the presence of saline and left lever choice in the presence of drug; the positions were reversed for the other half of the animals. The bar-press requirement for each reinforcer was gradually raised to 32 (FR 32), after which discrimination training began by exposing animals to both levers simultaneously. Training sessions lasted 30 min and were conducted five days per week. Percent correct responding for each training session was calculated as the number of responses on the correct lever prior to the delivery of the first reinforcer divided by the total number of responses on both levers.

### 2.4. Testing procedure

Testing began when the mean performance of the group (percent correct) met a criterion of greater than 85% for 10 consecutive days. Two kinds of tests were conducted: In *substitution* tests, animals were given various doses of the training drug (APO or LSD) or one of the four ergots (below) and tested for lever selection under extinction conditions; they were removed from the box after 32 responses occurred on one lever or the other or after 30 min, whichever occurred first. In *antagonism* tests, animals were given a DA or 5-HT antagonist in addition to the training drug and were run under the same extinction conditions.

Performance during test sessions was expressed as the number of responses on the training drug-appropriate lever (LSD or APO) divided by the total number of responses during the test session. The order of the test drugs was random throughout the study; at least one drug training session and one saline session occurred before each test.

### 2.5. Pharmacological procedure

All injections were given i.p. in a vol of 1 ml/kg for rats in the LSD group and 0.5 ml/kg for animals in the APO group. APO HCl (Sigma), ergonovine maleate (Sigma), lergotrile mesylate (Lilly), BC-105 (pizotifen or pizotyline) (Sandoz) and haloperidol (McNeil) were dissolved in deionized water. Lisuride hydrogen maleate (Schering AG) and d-LSD bitartrate (NIDA) were dissolved in saline. Bromocriptine (CB-154) (Sandoz) was dissolved in a minimum amount of 100% ethyl alcohol and diluted with deionized water. APO

and lergotrile were injected at 30 min intervals before testing; lisuride and LSD were given at 15 min intervals; bromocriptine was given at 60 min intervals; the antagonists BC-105 and haloperidol were given 60 min before testing. Ergonovine was given at 15 min before testing in the LSD group and at 30 min before testing in the APO group.

### 2.6. Data analysis

The data were analyzed using a one-tailed, correlated t-test which compared performance of each subject following a given test compound with that recorded during the immediately preceding training drug session. Only data obtained from animals which performed above 85% correct on both drug and saline training days and emitted at least 10 lever-presses on the test day were included in these analyses. A test compound was not considered to have substituted for the training drug if the t-values for all doses of the compound tested were significantly different from the training drug at $P < 0.05$.

## 3. Results

Discriminations were acquired rapidly; the average number of sessions required to meet criterion (10 consecutive sessions above 85% correct) was 15 for animals in the APO and 23 for animals in the LSD group.

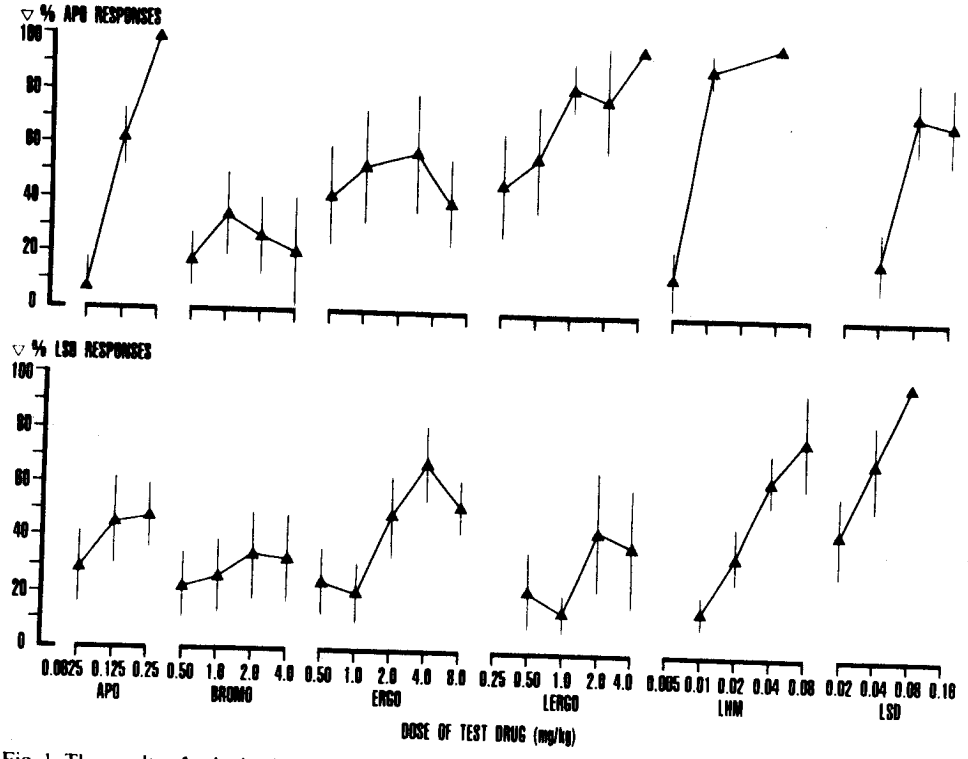


Fig. 1. The results of substitution tests with apomorphine (APO), bromocriptine (BROMO), ergonovine (ERGO), lergotrile (LERGO), lisuride (LHM) and LSD in rats trained to discriminate either 0.25 mg/kg APO from saline (*top panel*) or 0.08 mg/kg LSD from saline (*bottom panel*). The two highest doses of ERGO and the highest dose of LSD disrupted responding in 4 of 8, 5 of 8 and 6 of 9 animals, respectively; the highest doses of ERGO, LERGO and LHM suppressed responding in 9 of 18, 7 of 11 and 12 of 17 LSD-trained animals.

Results of substitution tests in the APO group are shown in fig. 1 (top). The APO cue was dose-dependent in that the percentage of drug lever responding decreased as the test dose of APO decreased. Neither bromocriptine (0.50–8.0 mg/kg) nor ergonovine (0.50–8.0 mg/kg) substituted for APO. Lergotrile, lisuride and LSD substituted for the APO cue in a dose dependent fashion (peak effects were 84% at 1.0 mg/kg of lergotrile, 91% at 0.01 mg/kg of lisuride and 75% at 0.08 mg/kg of LSD).

Fig. 1 (bottom) also shows the results of substitution tests in the LSD group. As in the APO group, the LSD cue was dose-dependent. Neither APO (0.0625–0.25 mg/kg), bromocriptine (0.50–8.0 mg/kg), ergonovine (0.50–8.0 mg/kg) nor lergotrile (0.50–8.0 mg/kg) substituted for LSD; the only ergot (besides LSD itself) that substituted (79%) was lisuride.

The results of antagonism tests are shown in table 1. The APO cue was blocked completely by 0.05 mg/kg haloperidol but not by 3.0 mg/kg BC-105. The LSD cue and the substitution of LSD for APO were blocked by 3.0 mg/kg BC-105; neither 0.05 mg/kg nor 0.10 mg/kg haloperidol completely blocked the substitution of LSD for APO; however, there was a decrease in the percentage of APO-lever responding following treatment with the combination of haloperidol and LSD.

## 4. Discussion

The results of this research confirm previous reports that the discriminative stimulus (DS) effects of APO and LSD are mediated specifically by direct activation of DA and 5-HT receptors, respectively (Colpaert et al., 1975, 1976; Kuhn et al., 1978; White and Appel, 1982c). Thus, the DA antagonist haloperidol (Janssen, 1967) completely blocked the APO cue but had no effect on the LSD cue whereas the 5-HT antagonist BC-105 (Lance et al., 1970) blocked the LSD cue but had no effect on the APO cue. Moreover, many other DA antagonists from different chemical classes (butyrophenone, diphenylbutalamine, phenothiazine, thiothiazine) antagonize the APO (Colpaert et al., 1976) but not the LSD cue (Kuhn et al., 1978).

The substitutions of lergotrile and lisuride for APO demonstrate that the discriminable effects of these ergots are related to their DA agonist properties (Silbergeld et al., 1979; Walters et al., 1979). Furthermore, their relative potencies (lisuride > APO > lergotrile) agree with their potencies as inhibitors of DA cell firing in the substantia nigra (Walters et al., 1979) and as inhibitors of [$^3$H]spiroperidol binding in rat caudate homogenates (Seeman, 1981). In addition, the same potency order was seen in rats trained to dis-

TABLE 1

Results of tests involving antagonists. n/N indicates number of rats responding (n) of those tested (N).

| Substitution drug | Dose (mg/kg) | Antagonism drug | Dose (mg/kg) | % Drug-lever-responding (± S.E.M.) | n/N |
|---|---|---|---|---|---|
| *LSD (0.08 mg/kg) group* | | | | | |
| BC-105 | 3.0 | | | 0 | 24/24 |
| LSD | 0.08 | BC-105 | 3.00 | 16 ± 7 | 21/21 |
| *Apomorphine (0.25 mg/kg) group* | | | | | |
| BC-105 | 3.00 | | | 5 ± 3 | 7/7 |
| Haloperidol | 0.05 | | | 0 | 7/7 |
| Apomorphine | 0.25 | BC-105 | 3.00 | 97 ± 2 | 7/7 |
| Apomorphine | 0.25 | Haloperidol | 0.05 | 0 | 7/7 |
| LSD | 0.08 | BC-105 | 3.00 | 1 ± 1 | 6/6 |
| LSD | 0.08 | Haloperidol | 0.05 | 68 ± 15 | 6/6 |
| LSD | 0.08 | Haloperidol | 0.10 | 55 ± 15 | 6/7 |

criminate lisuride from saline (White and Appel, 1982b).

In contrast to lergotrile and lisuride, bromocriptine and ergonovine failed to mimic APO. The negative finding with bromocriptine is particularly surprising in view of reports that lergotrile, lisuride, bromocriptine and APO have similar (DA agonist) properties in both rats (Keller and DaPrada, 1979) and humans (Goldstein et al., 1978; Calne, 1978). Possibly, the lack of effect of bromocriptine in the present study was due to the doses employed (although unpublished observations in this laboratory indicate that 16 mg/kg is also ineffective) or to a delayed onset of action due to slow absorption (Bannon et al., 1980; Fuxe et al., 1978; Horowski, 1979; Keller and Da Prada, 1979). However, it should be noted that bromocriptine elicits a different spectrum of pharmacological effects than do lisuride, lergotrile and APO under some conditions (Fuxe et al., 1978; Horowski, 1978; Ögren et al., 1979; Ungerstedt et al., 1981) and it is possible that the discriminable effects of bromocriptine are, in fact, different from those of APO, lisuride and lergotrile. The failure of ergonovine to substitute for APO suggests that DA agonism is not intricately involved in the discriminable effects of this drug, although there are reports that ergonovine can both activate and inhibit mesolimbic DA receptors when injected directly into the nucleus accumbens (Cools, 1978).

The inability of APO to substitute for LSD is consistent with previous findings that APO elicits 30–50% LSD-lever responding which is not related to either the test dose of APO or the dose of LSD used to establish the discrimination (Kuhn et al., 1978; White and Appel, 1982c). However, the finding that, in APO trained animals, LSD substitutes partially (70–80%) for APO agrees with results from other assays that LSD is a *weak* DA agonist in vivo (Christoph et al., 1978; Kehr and Speckenbach, 1978; Kelley and Iversen, 1975). Thus, the DA agonist effect of LSD may become evident in the drug discrimination procedure only when rats are trained to 'attend' to DA receptor activation. Moreover, this effect is 'secondary' to the action of LSD at 5-HT receptors since (1) BC-105 completely blocks both the LSD cue and the substitution of LSD for APO, and (2) the substitution of LSD for APO was only partially antagonized by haloperidol.

The ability of lisuride to substitute partially for LSD (79%) confirms a previous report from our laboratory that this ergot can produce an LSD-like DS (White and Appel, 1982a); in fact, higher doses of lisuride (0.16 mg/kg) can produce greater substitution (90%). These results are in accordance with the fact that lisuride acts as a 5-HT as well as a DA agonist (Kehr, 1977; Pieri et al., 1978; Rogawski and Aghajanian, 1979; Rosenfeld and Makman, 1981). The finding that lisuride substitutes for APO to a greater extent than for LSD confirms the hypothesis that the DS properties of lisuride are mediated primarily by DA receptors and that 5-HT systems play a 'secondary' role (White and Appel, 1982a, b).

The dose-dependent partial substitution of ergonovine for LSD closely resembles that produced by another ergot derivative, methysergide (Colpaert et al., 1979). Thus, like methysergide (Colpaert et al., 1979), ergonovine is probably a partial 5-HT agonist in the central nervous system. It is also interesting that both ergonovine (Bigwood et al., 1979; Jarvick, 1955) and methysergide (Hale and Reed, 1962) are sometimes hallucinogenic at high doses. The lack of substitution for LSD by bromocriptine and lergotrile indicates that the discriminable effects of these ergots do not involve 5-HT agonist actions.

## Acknowledgements

This research was supported by USPHS Research Grant 9 R01 DA 02543, from the National Institute on Drug Abuse. We thank K.A. Cunningham for assisting in manuscript preparation, A.B. White for drafting the figures, and the following for their gifts of drugs: Dr. H. Ahrens of Schering AG for lisuride hydrogen maleate, K.D. Roskaz of Sandoz for BC-105 and bromocriptine, M.F. Ralson of McNeil for haloperidol, and Drs. R.J. Hosley and R.W. Fuller of Lilly for lergotrile mesylate.

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