Lisuride and Other Dopamine Agonists

Basic Mechanisms and Endocrine and Neurological Effects

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Pharmacological Effects of Lisuride and Their Potential Role in Further Research

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The aim of this chapter is not to review the pharmacological or clinical effects of lisuride, which are now described in more than 200 publications, but to focus on aspects of this compound that are not covered in detail by the other authors of this volume. In particular, attention is given to some aspects related to the high affinity of lisuride for dopamine receptors, which has led to its use not only as a standard for the development of new compounds, but also for the investigation of many biological systems where dopaminergic mechanisms are known or suspected to be involved. This is followed by a brief discussion of the very complex interaction of lisuride with serotonergic systems and focuses mainly on the unique mounting behavior which can be provoked by high doses of lisuride in rats and its possible use as a pharmacological test for postsynaptic serotonergic agonists. Finally, a few studies are mentioned regarding another interesting property of lisuride—its strong autofluorescence *in vitro* and *in vivo*, which may become an interesting instrument for future studies.

BACKGROUND

The synthesis of lisuride (also called lysenyl or mesorgidine during its early investigation) and its peripheral antiserotonin effects were reported by the late Mieroslav Semonský (38), a pioneer in the chemistry and biology of centrally acting ergot derivatives. Since then, lisuride has been studied in the preventive treatment of migraine attacks (32) in a way similar to that of other peripheral serotonin antagonists of the ergoline type (methysergide) or nonergoline type (pizotifene).

Subsequently, central nervous system (CNS) effects of lisuride, which were described as "similar to amphetamine and, to a smaller extent, minor tranquilizers," were postulated based on a "pharmaco-EEG" method (22). In 1975 and the following years, we reported our observation—which in part was derived from our earlier investigation of the pharmacology of apomorphine—that lisuride acts as a strong, direct dopamine agonist with prolactin-lowering properties in animals and humans (13,16–18). This observation was confirmed by biochemical and neuro-

physiological observations and led to the investigation of lisuride in the treatment of hyperprolactinemia and acromegaly (26), prevention of postpartum lactation (5,14), and finally treatment of parkinsonism (11,25,35) and other related conditions, where dopaminergic and prolactin-lowering activity may be of clinical usefulness.

MATERIAL AND METHODS

Prolactin Study

The prolactin-lowering effect of ergot derivatives was studied as described earlier (13) in female Wistar rats weighing 180 to 220 g. After pretreatment of intact rats with reserpine (2 mg/kg i.p.) 20 to 24 hr before the experiments, animals were given the compounds by gastric tube, and blood was obtained by decapitation 2 hr after administration. Serum was frozen until assessed using NIAMDD radioimmunoassay materials for rat prolactin determination.

Studies of Mounting Behavior

Juvenile female Wistar rats weighing 80 to 120 g were used for the mounting behavior studies (K. Schwarz, Schering AG). In climatized rooms with constant humidity and day–night rhythm (lights on at 6 a.m., lights off at 6 p.m.), rats were housed as groups with the exception of the *p*-chlorphenylalanine (pCPA)-treated animals. Food (Altromin) and water was supplied *ad libitum*.

For the recording of mounting behavior, groups of five animals were transferred into a new environment (acrylic glass cage, 27 × 45 × 14 cm, containing neither food nor water, but straw as usual) immediately after treatment with lisuride, in a random order. Mounting behavior was scored as positive by an experienced observer when one animal placed its forepaws on the neck of another.

The frequency of mounting behavior per experimental group was registered at 10-min intervals during a period of 90 min. Each experiment was repeated at least once.

Compounds

Lisuride hydrogen maleate (Spofa, Prague), *d*-LSD bitartrate (Spofa, Prague) and BOL-148 (2-bromo-LSD, Sandoz AG, Basel) were used as freshly prepared solutions in 0.9% NaCl and injected subcutaneously. Drug doses were expressed in terms of the corresponding base. pCPA methylester was dissolved in a 10% (v/v) solution of Cremofor EL (polyethoxylated caster oil, BASF, Ludwigshafen) and injected at a dose of 100 mg/kg i.p. over 3 days before the experiments. pCPA-treated rats were housed individually until mounting behavior was studied. Bromocriptine mesylate (Sandoz AG, Basel) was dissolved in a few drops of absolute ethanol and diluted with a solution of tartaric acid as described earlier (13).

RESULTS AND DISCUSSION

Dopaminergic and Prolactin-Lowering Activity

The high activity of lisuride as a dopamine agonist with prolactin-lowering properties is reflected by many *in vitro* results reported in this volume. In many previous publications lisuride was the most potent dopamine agonist among all compounds tested (2,6,8,12,24,29,33,36). Its receptor affinity and other binding characteristics, which resemble those of spiroperidol (7), seem to be due to the interaction with dopamine as well as serotonin receptors. This high affinity of lisuride makes the compound an interesting tool for receptor studies. It is also conceivable that lisuride could displace some dopamine antagonists with lower receptor affinity from the dopamine receptors and thereby reduce side effects or effects of these compounds.

The dopamine receptor affinity of lisuride is in good correlation with its strong biological effects on dopaminergic systems. For example, Fig. 1 shows the prolactin-lowering effect of different oral doses of lisuride and bromocriptine in female rats pretreated with reserpine (in order to achieve uniformly elevated prolactin levels irrespective of fluctuations during the rat estrous cycle as described earlier). In this experiment, lisuride 0.01 mg/kg strongly reduces prolactin levels, whereas a similar suppression in the case of bromocriptine is observed only at 0.1 mg/kg p.o.

This at least 10 times higher activity of lisuride is consistent with a similar difference in humans, where lisuride 0.2 mg p.o. can be considered to be equipotent to 2.5 mg bromocriptine. Similarly, the oral LD_{50} of lisuride in rats is lower than in the case of bromocriptine. In this context it is striking that in a 2 years' carcinogenicity studies in rats treatment with lisuride even at sublethal oral doses did not result in endometrial tumors (G. Schuppler, *personal communication*), as they have been reported in the case of bromocriptine (19). Although the role of elevated prolactin levels in a proportion of old rats in preventing permanent estrus (which causes an unopposed estrogen effect on the endometrium) is quite probable (19), other explanations for this difference must be considered, e.g., the hypothesis of a shorter duration of the effects of lisuride under these conditions.

Whereas lisuride is approximately 10 times more potent than bromocriptine as a prolactin-lowering agent, it is up to 100 times more potent as a dopamine agonist in animal models for Parkinson's disease. Herken and his co-workers reported an ED_{50} of 0.0026 mg/kg i.p. for lisuride in reserpine-induced muscular rigidity in rats, whereas bromocriptine had an ED_{50} of only 0.211 mg/kg i.p. (28). When studying interaction with monoamine-depleting compounds and dopamine antagonists, similar and sometimes even qualitative differences have been observed by our group (15,20).

It is not clear whether this greater difference reflects a poorer penetration of bromocriptine into the brain, a different type of effect at the level of different dopamine receptors (e.g., different affinities for pre- and postsynaptic receptors), or a consequence of additional effects on other systems—serotonergic, for example. More controlled clinical studies are necessary to evaluate the relevance of this difference between the two drugs.

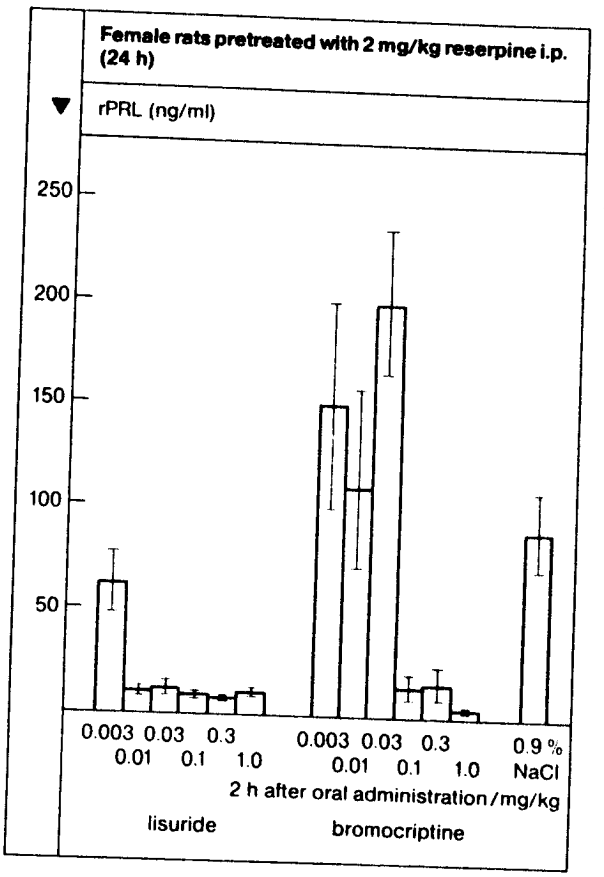

FIG. 1. Serum prolactin levels ($\bar{x} \pm$ SEM) in reserpinized female rats 2 hr after oral administration of various doses (0.003 to 1.0 mg/kg) of lisuride, bromocriptine, or saline.

Interaction with Serotonergic Systems

Lisuride is a strong antagonist of serotonin-mediated peripheral effects both *in vitro* and *in vivo* (32). As in the case of dopamine receptors, lisuride has a very high binding affinity for serotonin receptors (30). In biochemical studies lisuride has been classified sometimes as a receptor agonist (23). In view of pharmacological data describing lisuride as a functional serotonin antagonist at least in some systems (4,17,32), a preferential effect of lisuride as an agonist at presynaptic serotonin receptors has been proposed (31). Stimulation of these receptors, indeed, results in a functional inhibition of serotonergic neurotransmission.

As is rather often the case with serotonin and ergolines, it is evident that the biochemical definition of an effect depends very much on the biological systems tested and that compounds can easily act as an agonist at one receptor site and as

an antagonist in another system. In addition, drugs which were used to define serotonergic mechanisms are not very specific, and the interaction of ergolines with many monoaminergic systems makes the situation quite complex. Also in the clinical use of lisuride, the interpretation of the role of its antiserotonergic properties is difficult due to the lack of well-defined clinical symptoms or diseases related to serotonin.

Unfortunately, our expectations of some striking differences between lisuride and bromocriptine (which has much lower affinity for serotonergic systems) in the clinical effects or side effects (important differences, for example, in the incidence of psychiatric side effects in parkinsonian patients) have been frustrated so far, and further controled studies are certainly needed. Obviously, dosage is an important factor in pharmacological and clinical studies, as demonstrated in Table 1.

Mounting Behavior

The similarities between lisuride and *d*-LSD, in regard to chemical, biochemical, electrophysiological, and pharmacological effects, have led to the proposal that further investigation of the nonhallucinogenic lisuride and its interaction with the serotonergic system as compared with *d*-LSD may result in a better understanding of the mechanism of hallucinations induced by *d*-LSD in humans (31). We therefore studied mounting behavior induced by lisuride, as this is a unique effect of lisuride not shared by *d*-LSD.

We found that mounting behavior in juvenile female rats, a typical behavioral effect of lisuride (4), which is similar to the action of pCPA, (9) is inhibited by low doses of *d*-LSD. When given as a single subcutaneous injection to groups of five juvenile female rats, lisuride elicited frequent mounting behavior in a dose range from 0.1 to 0.78 mg/kg (Fig. 2). The effects were clearly dose-dependent. At doses above 0.5 mg/kg, a few animals had strong movement disorders or even died with symptoms similar to those seen with amphetamine intoxication. Therefore we used a standard dose of lisuride 0.5 mg/kg s.c. for further testing. At this dosage, mounting behavior started within some minutes after the injection, reaching a maximum at 40 to 60 min. Effects lasted for about 90 min.

Mounting behavior was preceded by licking of the neck or genital sniffing in many animals and was often accompanied by piloerection and Straub phenomenon. Pelvic thrusting movements were rare in our rat population, although offensive-defensive postures were sometimes observed. Often, all five rats tried to mount each other at the same time.

The typical mounting behavior caused by lisuride was clearly antagonized by a simultaneous injection of *d*-LSD at the same dose (Fig. 3). Instead of mounting behavior, some animals displayed head shaking, tremors, vibrations of the vibrissae, and other symptoms of the so-called LSD syndrome.

The inhibitory effect of *d*-LSD on the lisuride-induced mounting behavior was dose-dependent (data not shown). A similar degree of inhibition at comparable dose levels could be observed after simultaneous injection of BOL-148 (Fig. 4).

TABLE 1. *Simplified pattern of lisuride effects related to dosage*

Type of activity	Biochemical test *in vitro*	Neurophysiological effect	Pharmacological effects in rats	Clinical use and average oral dosage per day
Serotonin partial agonist activity	Agonist binding to serotonin receptors at very low concentrations	Inhibition of raphé unit firing rate at very low dosage		Prevention of migraine attacks (0.075 mg)
Dopamine agonist activity	Inhibition of prolactin secretion		Prolactin-lowering effect and inhibition of lactation at low doses	Treatment of hyperprolactinemic states (0.3–5.0 mg) and inhibition of lactation (0.4–0.6 mg)
	Agonist binding to dopamine receptors at low concentrations	Inhibition of substantia nigra cell firing rate at low dosage	Antagonism of reserpine—immobility at low dosage	Antiparkinson activity (1.0–5.0 mg)
α-Adrenolytic activity	Antagonist binding to NE receptors at high concentrations	Inhibition of locus coeruleus cell firing rate at intermediate dosage	Inhibition of NE toxicity at high dosage	
β-Adrenolytic activity	Antagonist binding to β-adrenergic receptors at high concentrations			

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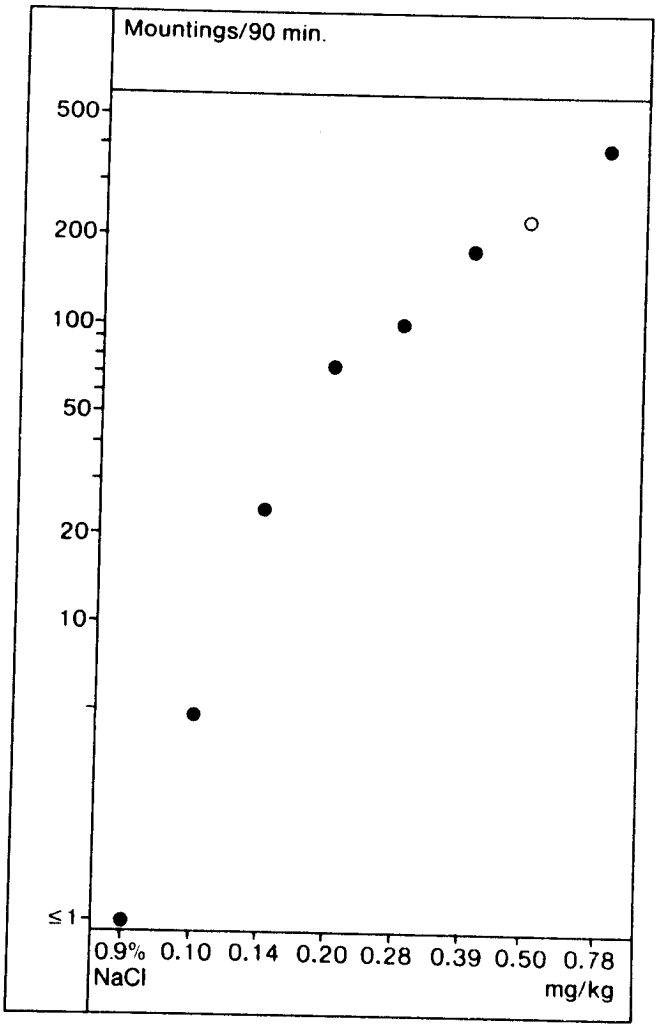

FIG. 2. Dose-effect relationship of lisuride-induced mounting behavior. Groups of five juvenile female rats were treated with various doses of lisuride, and the total number of mounting episodes was registered over a period of 90 min.

Mounting behavior induced by chronic treatment with pCPA was not affected by treatment with lisuride. In contrast, rather low doses of *d*-LSD had a clearly inhibitory effect (data not shown).

On the basis of results obtained with the serotonin synthesis inhibitor pCPA combined with dopaminergic agonists, it has been claimed that sexual behavior in rats is regulated by an inhibitory serotonergic system and an activating dopaminergic system (9). The effects of lisuride described in this study are in agreement with this hypothesis: Based on biochemical (31) and electrophysiological (34) results, a

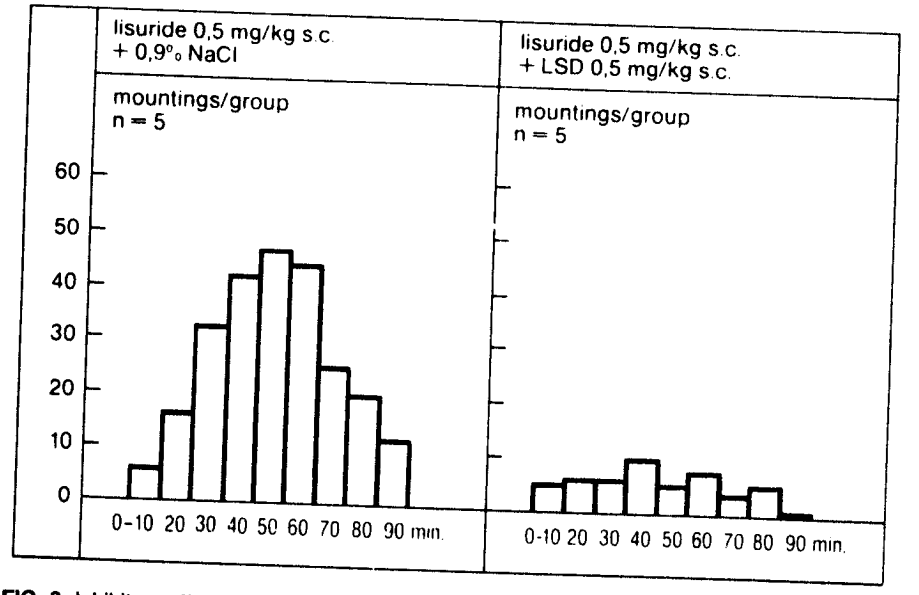

FIG. 3. Inhibitory effect of *d*-LSD on lisuride-induced mounting behavior in juvenile female rats (groups of five). The total number of mounting episodes per group is given at 10-min intervals.

functional serotonin antagonistic effect of lisuride in the CNS has been proposed; moreover, the dopaminergic action of lisuride has been clearly demonstrated by pharmacological and clinical studies.

Mounting behavior in rats has not been observed after injection of *d*-LSD. On the contrary, *d*-LSD strongly inhibits this type of behavior induced by treatment with lisuride or pCPA, as shown by our results. This indicates an important difference between lisuride and *d*-LSD with respect to the serotonergic or dopaminergic mechanisms involved in mounting behavior in rats.

If one accepts the hypothesis of a serotonergic–dopaminergic balance regulating sexual behavior in rats, the inhibitory effect of *d*-LSD on this phenomenon should be due to either a functional activation of serotonergic mechanisms or an inhibition of dopaminergic neurotransmission.

An antidopaminergic effect of *d*-LSD at high doses has indeed been discussed on the basis of biochemical results (27). It is also interesting to note that *d*-LSD has no emetic effect in dogs, an effect considered to be an expression of dopaminergic activity (17). On the contrary, *d*-LSD even blocks the emetic action of apomorphine (27), and therefore an antidopaminergic effect of *d*-LSD at some doses cannot be excluded. It is, however, more likely that this compound at the low doses used in our experiment acts by an activation of postsynaptic serotonin receptors, as does BOL-148, a compound for which no antidopaminergic effects have been described (27). A stimulatory effect on postsynaptic serotonin receptors has been proposed in the case of *d*-LSD, as it has for lisuride (23). The lack of efficacy of lisuride on the mounting behavior produced by serotonin depletion in pCPA-treated rats, however, is strong evidence against an activation of postsynaptic serotonin

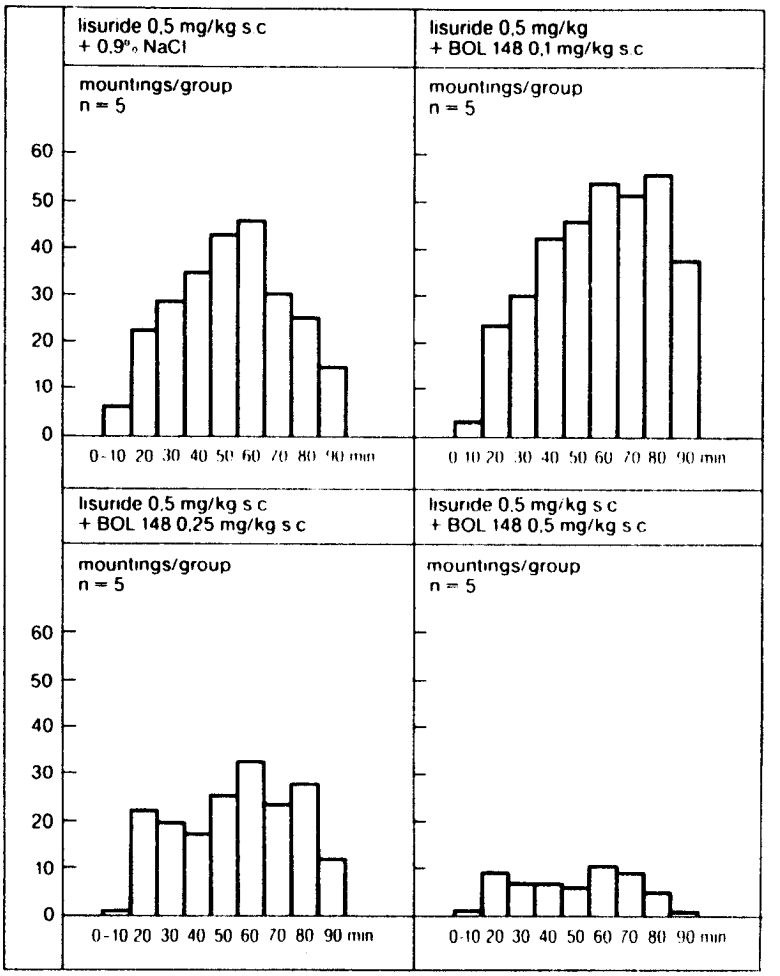

FIG. 4. Dose-dependent inhibition of lisuride-induced mounting behavior by BOL-148 in juvenile female rats. The total number of mounting episodes per group is given at 10-min intervals as in Fig. 3.

receptors by lisuride, at least in the doses tested and within our experimental conditions.

In conclusion, our results demonstrate a clear-cut pharmacological difference between lisuride and *d*-LSD in regard to the induction of inhibition of mounting behavior in rats. This difference must be taken into account in the discussion of the role of the serotonergic system in the pathogenesis of hallucinations. On the basis of our data, lisuride seems to be a "purer" functional antagonist of serotonergic neurotransmission. This could be due to a selective affinity of this drug to presynaptic serotonergic receptors.

Development of drugs with such a mode of action could lead to a new and more

"physiological" type of inhibitor of monoamine neurons as compared with conventional postsynaptic receptor blocking agents. Finally, the inhibiting effect of *d*-LSD and BOL-148 on lisuride-induced mounting may indicate that this phenomenon can be used as a simple and reliable pharmacological tool for the detection of more specific agonists of postsynaptic serotonin receptors. Such a screening test consists simply of injecting the test compound before giving a standard dose of lisuride to groups of young rats. When mounting behavior is inhibited, a subsequent test for apomorphine antagonism will help differentiate between serotonin agonists and dopamine antagonists.

In addition to these pharmacological aspects, lisuride-induced mounting behavior is very helpful for studying interactions between brain and gonads. In contrast to previous views about the role of hormones in sexual behavior, experiments with lisuride in rats have shown that mounting behavior can be induced independent of the sex of the animals, the sex and even species of the partners, and the hormonal situation. Lisuride-induced mounting behavior was not influenced by pre- or postnatal hormone treatment or castration (i.e., ovariectomy) but only by age (21).

Ahlenius and his co-workers (1) have shown that not only mounting behavior, but also intromission and ejaculation, can be restored in male castrated rats by treatment with lisuride. All these data indicate that, at least in rats, gonadal hormones may have important priming and facilitating effects but that the neuronal systems responsible for sex-related complex behavioral patterns can be activated quite independently, simply by treating the animals with lisuride.

Interaction of Lisuride with Other Systems

The affinity of lisuride for dopamine receptors is clearly related to its clinical use. However, similar relationships are yet to be clearly established in the case of the serotonin system but can be expected from the concentrations and doses used in biochemical and pharmacological studies. In contrast, the inhibitory effect of lisuride on α-adrenergic receptors could be observed only at rather high concentrations (3), with the possible exception of α-receptors located on blood platelets, where lisuride is a very potent antagonist of epinephrine-induced aggregation (10). Finally, lisuride is the first ergoline derivative for which a β-adrenergic blocking effect has also been observed *in vitro*—at concentrations which were so high no clinical significance can be expected (3). The interactions of lisuride with monoamine receptors and their possible clinical relevance is summarized in Table 1.

The outstanding affinity of lisuride for monoamine receptors may also be of value for histological and cytological studies using autoradiography (37) or lisuride antibodies (F. El Etreby, *personal communication*). Due to its strong blue-violet autofluorescence (excitation wave length 240 nm, emission 310 nm), lisuride can be used also for staining and identifying cells, as proposed by Herken and his group (*personal communication*). If this fluorescence is caused by specific binding to some monoamine receptors, lisuride fluorescence labeling techniques can be developed for histochemical studies. The same holds true for the subsequent discovery

by Dorow that lisuride at concentrations of 10^{-5} to 10^{-6}M selectively induces its typical fluorescence in human and animal leukocytes (21).

CONCLUSION

The high affinity of lisuride for several monoamine receptor systems and their unique combination are not only the basis of the clinical use of lisuride but may also help improve our knowledge of these systems. Lisuride is a good tool for labeling and studying receptors and investigating their function. Its similarities and differences to *d*-LSD may lead to a better understanding of the mechanism of hallucination. Lisuride-induced mounting behavior in rats is of high interest for studying CNS–hormone relationships and may also become a simple test for detecting serotonin agonists. Lisuride fluorescence may be of value for identifying and differentiating cells.

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