European Journal of Pharmacology, 51 (1978) 157—166

DIFFERENCES IN THE DOPAMINERGIC EFFECTS OF THE ERGOT DERIVATIVES BROMOCRIPTINE, LISURIDE AND d-LSD AS COMPARED WITH APOMORPHINE

REINHARD HOROWSKI

Schering AG, Berlin/Bergkamen, Special Research Project Group, Müllerstrasse 170—178, D 1000 Berlin 65 (West), Germany

Received 3 January 1978, revised MS received 26 April 1978, accepted 12 June 1978

R. HOROWSKI, *Differences in the dopaminergic effects of the ergot derivatives bromocriptine, lisuride and d-LSD as compared with apomorphine*, European J. Pharmacol. 51 (1978) 157—166.

In normal mice, hypothermia induced by treatment with apomorphine or lisuride could be inhibited by pretreatment with sulpiride, whilst the stereotyped behaviour in these animals was not affected. In reserpine-pretreated mice, apomorphine, lisuride, d-LSD and bromocriptine restored motor activity at least in part, antagonised the hypothermia caused by reserpine, and, with the exception of bromocriptine, produced stereotyped behaviour. Only the effects caused by bromocriptine could be abolished completely by even very low doses of sulpiride, whilst high doses of this drug had no or only very little effect on the activity of the other dopaminergic agonists. Inhibition of tyrosine hydroxylase by α-methyl-p-tyrosine completely prevented the effects of bromocriptine, but affected only very slightly the effects of lisuride and d-LSD, and not at all the activity of apomorphine. These results clearly demonstrate that the same type of dopaminergic activation produced by ergot derivatives in mice can be obtained by two different mechanisms, one of which in the case of bromocriptine is easily inhibited by sulpiride at low doses. If one accepts the hypothesis of a high affinity of this drug to presynaptic receptors, then our data could be explained by the hypothesis that bromocriptine exerts its effects in our test system via an inhibitory effect on these presynaptic dopamine receptors, and that this effect can be counteracted by sulpiride. Other possibilities, however, are not excluded.

Dopaminergic activity Lisuride d-LSD Bromocriptine

1. Introduction

In rodents, dopamine depletion induced by reserpine causes strong motor depression and tremor (Carlsson, 1959) which can be counteracted by the dopamine precursor L-DOPA. When it was found that, in humans, Parkinson's disease is a result of central dopamine deficiency (Ehringer and Hornykiewicz, 1960), reserpinised rodents became accepted as an animal model of this disease, and dopaminergic agonists such as L-DOPA and apomorphine were shown to be effective both as antagonists of reserpine-induced motor depression in rodents and in the treatment of Parkinson's disease (for review see Carlsson, 1972). Subsequently, ergot derivatives were also found to have dopaminergic activity, as in the case of bromocriptine (Corrodi et al., 1973), d-LSD (Fuxe et al., 1975) and lisuride (Horowski et al., 1975). These ergot derivatives also effectively antagonised reserpine-induced motor depression (Johnson et al., 1976; Fuxe et al., 1975; Horowski and Wachtel, 1976). One of these derivatives, bromocriptine, has also been found to have anti-Parkinson activity (Calne et al., 1976).

However, since dopamine as a neurotransmitter is not only involved in the maintenance of normal motor function, treatment with dopaminergic agonists also produces side effects which make these compounds intolerable to some patients with Parkinson's disease. One approach to improve this situation could be the development of dopaminergic agonists which are especially active in supersensitive systems, as has been reported for d-LSD (Fuxe et al., 1975) and perhaps,

for lisuride; such compounds should stimulate the supersensitive nigro-neostriatal pathways in Parkinson's disease at doses lower than those required for stimulation of receptors in areas where no denervation has occurred. Another possibility was proposed (Corsini et al., 1976) as a result of the demonstration that pretreatment with the classical neuroleptic haloperidol antagonised all effects of apomorphine in humans, whereas, after pretreatment with sulpiride, the anti-Parkinson activity remained and only side effects such as nausea and emesis were prevented.

Against this background we studied the effect of pretreatment with sulpiride on different pharmacological effects of the ergot derivatives bromocriptine, d-LSD and lisuride in mice as compared with apomorphine, in order to see whether the action of these drugs could be influenced by sylpiride in the same way as has been described for apomorphine (Puech et al., 1976).

In intact animals, apomorphine and lisuride produce strong stereotyped behaviour and hypothermia, effects which could be prevented by haloperidol (Horowski and Wachtel, 1976). However, since bromocriptine and d-LSD did not have such clear effects in normal mice, all drugs were tested further in animals pretreated with reserpine, as dopaminergic drugs are known to induce stereotyped behaviour, restore motor activity — at least in part —, and increase the low body temperatures in animals so pretreated. Finally, we used reserpinised mice after additional pre-treatment with the catecholamine synthesis inhibitor α-methyl-p-tyrosine in order to see whether intact catecholamine synthesis was necessary for the pharmacological effects of the four ergot derivatives.

2. Materials and methods

2.1. Drugs and solutions

The following drugs were used: lisuride hydrogen maleate (Spofa, Prague), bromocriptine (Sandoz A.G., Basle), D-lysergic acid diethylamide (d-LSD, Spofa, Prague), apomorphine hydrochloride (Sandoz, A.G., Basle), sulpiride (Delagrange, Paris), reserpine hydrochloride (as Serpasil®, Ciba/Geigy, Basle), α-methyl-p-tyrosine methylester hydrochloride (H44/68 Hässle A.B., Gothenburg). Most substances were dissolved in 0.9% saline. Reserpine hydrochloride was used as Serpasil® ampoules containing 1 mg/ml. Sulpiride was dissolved in a 10% solution of Cremofor EL (polyethoxylated castor oil, BASF, Ludwigshafen) in saline. Bromocriptine was dissolved in a few drops of ethanol and then diluted with 0.9% saline.

2.2. Administration

Apomorphine and the ergot derivatives lisuride, d-LSD and bromocriptine were given s.c., as they were more active via this route of administration. All the other drugs were administered i.p. All doses were calculated as the base and allocated to the animals at random in a volume of 0.2 ml per 20 g body weight.

2.3. Animals

Female NMRI mice weighing 18—25 g (Dr. Schwarz, Schering A.G. Berlin) were used. The animals received Altromin® as a standard diet and water ad libitum. 1 h before testing, the animals were placed individually into acrylic glass cages (9 × 19 × 9) in a diffusely illuminated room maintained at a temperature of 22 ± 1°C and at constant humidity.

2.4. Test methods

In some experiments, animals were pretreated with reserpine (10 mg/kg i.p. 20—24 h before testing) alone or in combination with α-methyl-p-tyrosine (250 mg/kg i.p., 2.5 h before the test drug) or with sulpiride (1 h before administration of the dopaminergic agonists).

Stereotyped behaviour was observed as described earlier (Horowski and Wachtel, 1976). The animals were observed in their

individual cages for 1 min for the detection of stereotyped behaviour (continuous licking, sniffing or gnawing movements for more than 30 sec within this time) by an experienced observer unaware of the previous treatment. This was especially easy in the reserpinised animals where no spontaneous activities interfered with the observation.

The motor activation in mice whose spontaneous activity had been abolished by pretreatment with reserpine was evaluated by the method of Vernier et al. (1962). Animals were exposed to an open field (60 × 45 × 7 cm) and scored positive for motor activity on covering a minimum distance of 30 cm within 1 min. Thus, for a positive score, no complete restoration of motor activity was required, but merely a minimal motor response to the new environment not seen in the cataleptic controls.

The body temperature of the animals was measured with an electric universal thermometer (ELLAB TE 3) 20 sec after the introduction of a rectal probe (RM 4). The drugs were tested as follows: apomorphine, lisuride, and d-LSD 30 min, bromocriptine 2 h after injection, since preliminary studies have shown optimal activity of the drugs under these conditions.

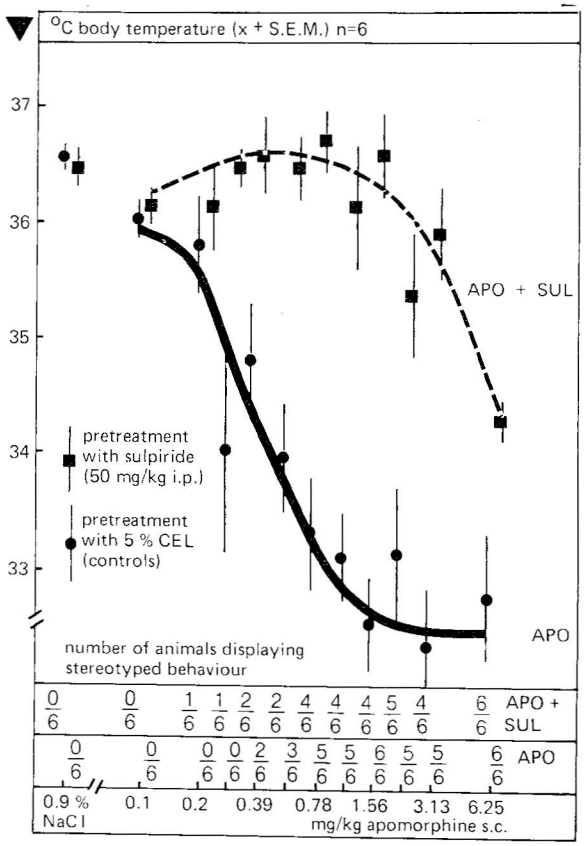

Fig. 1. Influence of pretreatment with sulpiride on apomorphine-induced hypothermia in mice.

2.5. *Statistics*

Statistical significance was evaluated using the Mann—Whitney U-test, while the median effective doses (ED_{50}) and 95% confidence limits were determined by probit analysis.

3. Results

3.1. *Intact mice*

In normal animals, only apomorphine and lisuride induced stereotyped behaviour and hypothermia in dose-dependent manner. Pretreatment with sulpiride (50 mg/kg i.p.) abolished the hypothermic effect of both compounds (figs. 1 and 2). After this treatment, maximally effective doses of both compounds (1.56 mg/kg apomorphine, 0.07 mg/kg lisuride) produced body temperatures which were again in the range of those of untreated animals. In contrast to this, the stereotyped behaviour induced by apomorphine and lisuride in the same animals was not affected at all by sulpiride.

3.2. *Mice treated with reserpine*

Apomorphine and lisuride induced stereotyped behaviour in mice treated with low doses of reserpine (ED_{50} of lisuride 0.18, (0.13—0.26) mg/kg s.c.). d-LSD also induced stereotyped behaviour, whilst this type of activity could not be observed after treatment with bromocriptine. All drugs restored motor

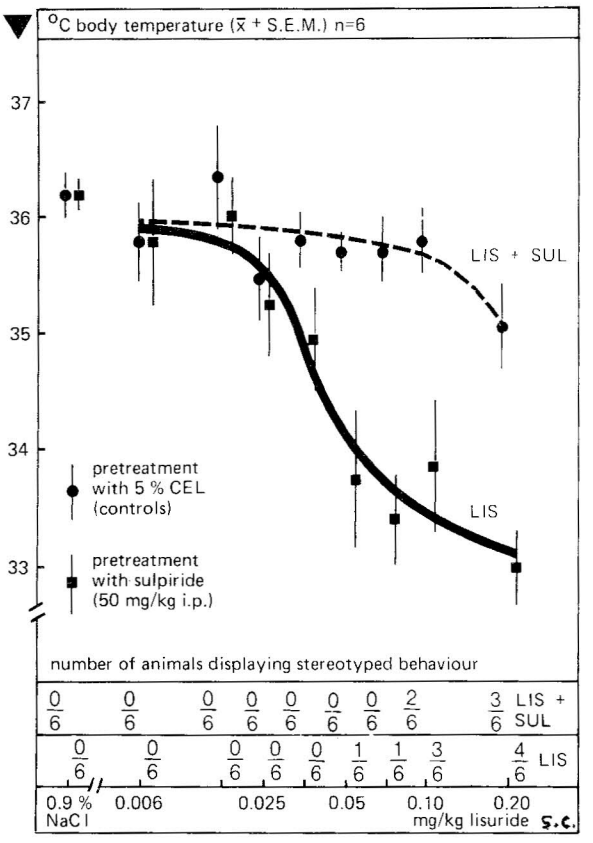

Fig. 2. Influence of pretreatment with sulpiride on lisuride-induced hypothermia in mice.

activity (not to the normal level but sufficiently, according to our criterion) and antagonised the reserpine-induced fall in body temperature. Bromocriptine was, however, active only after rather high dosages (ED_{50} for restoration of motor activity: 4.4 (2.3—8.6) mg/kg s.c.). As can be seen from fig. 3, pretreatment with low (1.56 mg/kg i.p.) and high (50 mg/kg i.p.) dosages of sulpiride completely antagonised the action of bromocriptine. The effects of apomorphine, d-LSD and lisuride were not or only very slightly affected or, in the case of body temperature, were increased even further.

Another experiment with bromocriptine showed that the dose-dependent increase in body temperature and motor activity caused by bromocriptine was virtually abolished by pretreatment with 50 mg/kg sulpiride given i.p. Stereotyped behaviour could not be observed in any of the animals (fig. 4).

Since even a low dose of sulpiride was effective in antagonising bromocriptine effects (see fig. 3), we checked whether the effect of sulpiride was dose-dependent (fig. 5). As can be seen, doses of sulpiride as low as 1.56 mg/kg were effective in reducing the bromocriptine-induced increase in body temperature in reser-

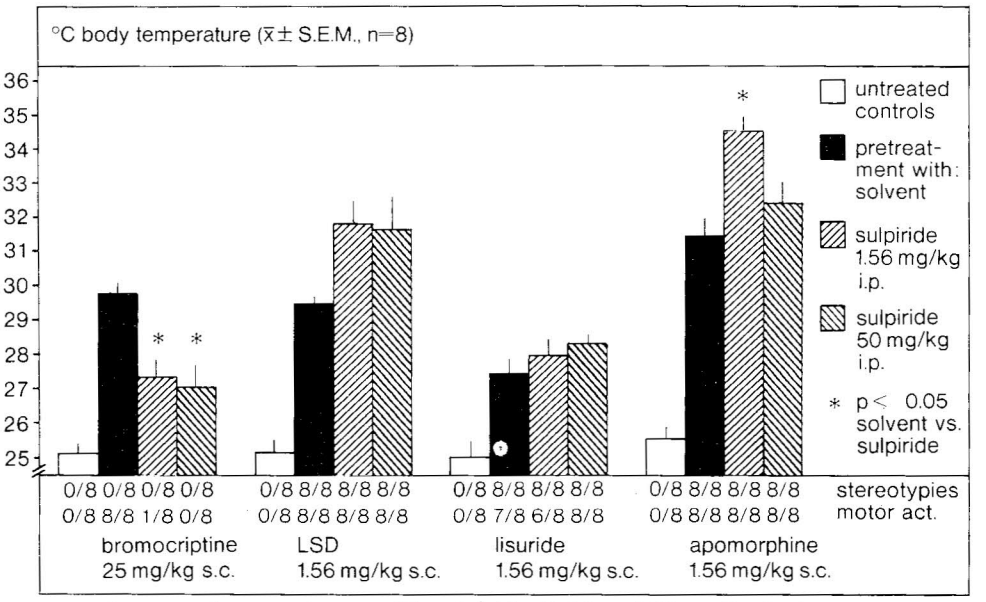

Fig. 3. Influence of pretreatment with sulpiride (1.56 and 50 mg/kg i.p.) on ergot effects in reserpinized mice.

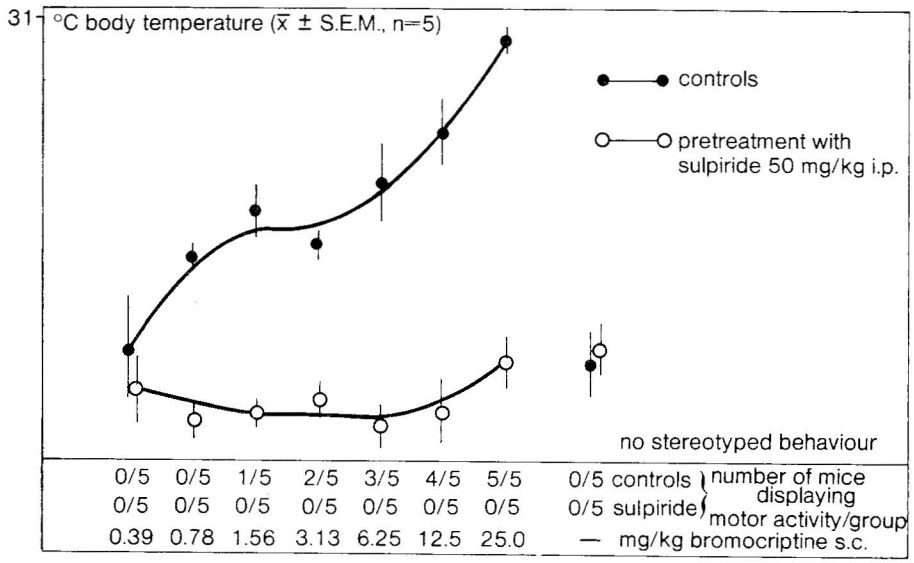

Fig. 4. Influence of pretreatment with sulpiride (50 mg/kg i.p.) on bromocriptine effects in reserpinized mice.

pinised mice, whilst even lower doses were effective in preventing the motor activation (ED_{50} 0.35 (0.19—0.62) mg/kg sulpiride i.p.).

In the case of lisuride, the dose-dependent effects of this compound in reserpinised mice could be reduced only very slightly by pretreatment with 50 mg/kg sulpiride i.p. (fig. 6). Even after this pretreatment, lisuride was highly active as a dopaminergic agonist because a dose as low as 0.55 mg/kg s.c. was still effective in all animals tested.

3.3. Mice treated with reserpine and α-methyl-p-tyrosine

The effect of additional pretreatment with the catecholamine synthesis inhibitor α-methyl-p-tyrosine was investigated in a fur-

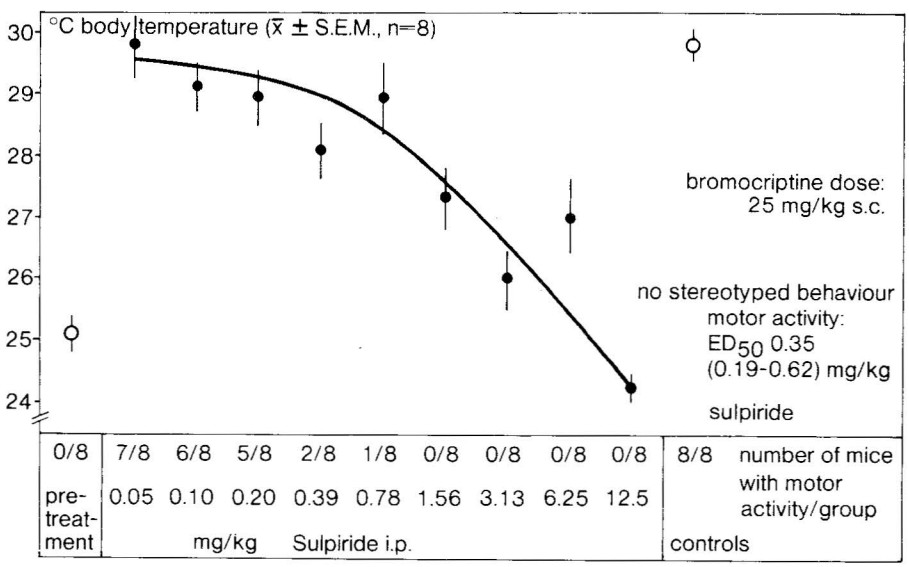

Fig. 5. Influence of pretreatment with different doses of sulpiride on bromocriptine effects in reserpinized mice.

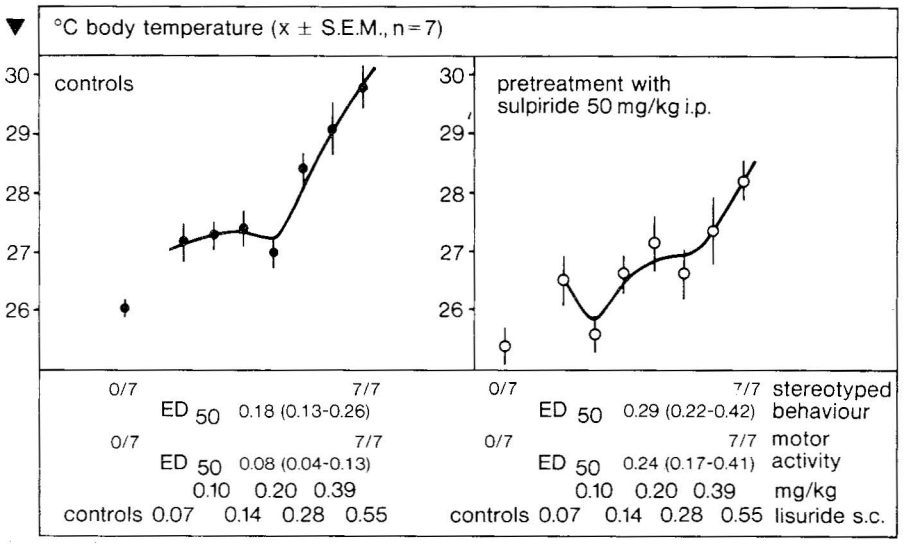

Fig. 6. Influence of pretreatment with sulpiride (50 mg/kg i.p.) on lisuride effects in reserpinized mice.

ther experiment, in which animals were treated with 0.1, 1.0 and 10.0 mg/kg apomorphine, lisuride, d-LSD and bromocriptine (fig. 7). It can be seen that the effects of bromocriptine were also completely abolished by this kind of pretreatment, whilst only the effect of the lowest dose of lisuride was affected and the activity of apomorphine was not affected at all. This was true of the effects of these drugs on body temperature as well as on motor activity and stereotyped behaviour. In the case of d-LSD, the effects on body temperature were reduced but not abolished, whilst motor activity and stereotyped behaviour were not affected.

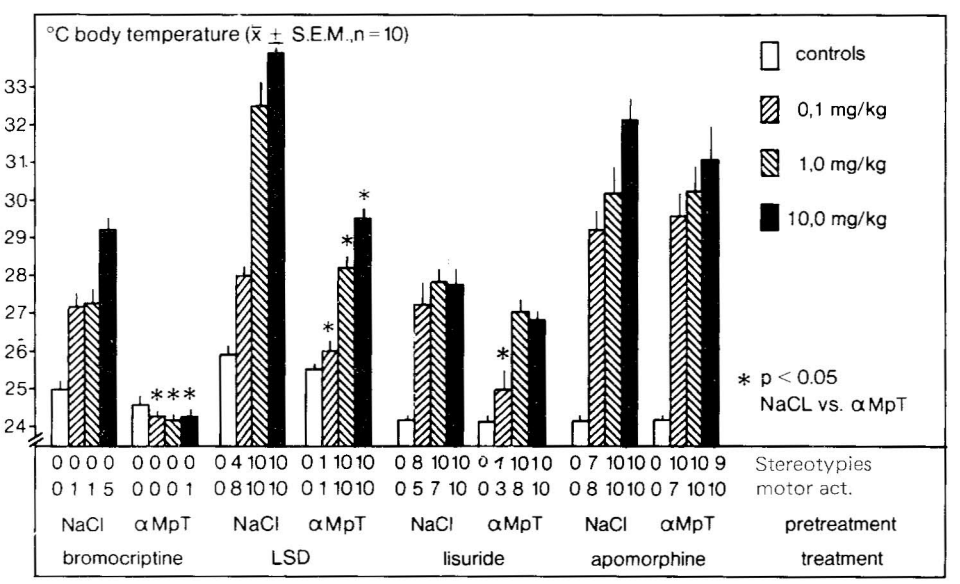

Fig. 7. Influence of pretreatment with α-methyl-p-tyrosine on ergot effects in reserpinized mice.

4. Discussion

Our results in normal mice confirm that sulpiride only inhibits some apomorphine effects whilst it does not affect others, e.g. stereotyped behaviour (Boissier et al., 1977). It is interesting that the same differences could be found with the ergot derivative lisuride.

If this holds for humans, an anti-Parkinson effect could probably also be maintained in the case of lisuride, others effects of the drug being prevented by simultaneous treatment with sulpiride or related compounds. It has been shown in preliminary human studies that the nausea and emesis induced by lisuride in some human volunteers could be inhibited by i.m. injection of 50 mg sulpiride; the prolactin-lowering effect of lisuride in humans was inhibited at the same time (Horowski et al., 1978).

Both the stereotyped behaviour and hypothermia induced in mice by apomorphine and lisuride are considered to be due to an effect on dopaminergic systems; both symptoms can be inhibited by the dopamine antagonist haloperidol (Horowski and Wachtel, 1976). The question which therefore remains is why only the hypothermic effect is affected by sulpiride. One possible explanation for this difference is that sulpiride may reach only those parts of the brain where the blood-brain barrier is unsufficient, as is the case in the hypothalamus and the chemoreceptor-trigger zone of the medulla oblongata. This hypothesis, however, is unlikely to be correct not only because in vitro data show that sulpiride is not effective in nigro-neostriatal dopaminergic systems (Trabucchi et al., 1975) considered to be the basis of the stereotyped behaviour, but also because our data from reserpinised mice do not support it in any way. Identical effects induced by dopaminergic agonists, i.e. restoration of motor activity or increase in body temperature, could be inhibited by sulpiride in the case of bromocriptine only and not in the case of lisuride, d-LSD or apomorphine. In this respect, it is important to remember that dopaminergic systems inside the blood—brain barrier (the nigro-neostriatal pathway as well as the nucleus accumbens) have been shown to be involved in the induction of motor activity.

Another possibility is that sulpiride can inhibit effects of the ergot derivatives on other systems e.g. serotonergic or noradrenergic mechanisms. This is again very unlikely, because all the effects we measured can also be induced by apomorphine, which can be regareded as being very specific for dopaminergic systems. Furthermore, no significant interactions of sulpiride with other monoaminergic systems have yet been reported.

On the basis of this, it seems likely that the dopaminergic agonists tested by us exert their pharmacological and also their clinical effects via different actions on dopaminergic mechanisms, only one of which can be blocked by sulpiride. Our data show that bromocriptine has a preferential effect of this type which is easily inhibited by sulpiride, while lisuride, apomorphine and d-LSD have a prominent effect on the other type of dopaminergic system which can not be blocked by sulpiride even in high doses.

It is very interesting in this context that apomorphine as an agonist and haloperidol as an antagonist strongly influence the dopamine-dependent adenylate cyclase whilst the effects of bromocriptine and sulpiride are much less pronounced or even absent (Spano et al., 1977; Trabucchi et al., 1976). A dual system of dopaminergic effects has been proposed by different authors (Carlsson, 1975; Cools and van Rossum, 1976). Carlsson (1977) has postulated that the stimulation of autoreceptors by dopaminergic agonists leads to an inhibition of the neuronal firing rate as well as to an inhibition of neuronal dopamine synthesis. It has been suggested that both bromocriptine and sulpiride have a preferential effect on this kind of receptor (Di Chiara et al., 1977; Trabucchi et al., 1975; Fuxe et al., 1977). The pharmacological data reported here do not appear to agree with this hypothesis, since bromocriptine produced effects

similar to those of apomorphine, i.e. restoration of motor activity and increase in body temperature, whereas one would expect an opposite effect on the basis of an activation of presynaptic receptors. One explanation for this could that bromocriptine is known to possess both agonist and antagonist properties (Goldstein et al., 1977) and that, in low doses, this drug can block the dopamine-induced activation of adenylate cyclase (Trabucchi et al., 1976). Thus it is quite possible that, in our experiments, bromocriptine was able to block the presynaptic receptors, thereby increasing neuronal activity with, as a result, the liberation of more dopamine into the synaptic cleft. On this basis it would be quite easy to understand that these effects of bromocriptine could be blocked by the inhibition of catecholamine synthesis with α-methyl-p-tyrosine, as shown in fig. 7, while the same effects caused by stimulation of postsynaptic dopamine receptors in the case of lisuride, d-LSD and apomorphine were not affected. In any case, the inhibition of the effects of bromocriptine could be used as a simple and sensitive pharmacological model for testing drugs with sulpiride-like activity — in contrast to the apomorphine-induced stereotypies which are good test systems only for classical neuroleptics.

If one accepts the hypothesis that there are two different dopaminergic systems which can both be activated by the classic dopamine agonist apomorphine while one is activated preferentially by bromocriptine and inhibited by sulpiride, then it is important to stress that this second type closely resembles the dopaminergic system inhibiting prolactin release, because both bromocriptine and especially sulpiride in low doses are highly effective in this system also (Horowski and Gräf, 1977).

From our results reported here and elsewhere it can be concluded that both bromocriptine and lisuride have prominent dop-

TABLE 1

Some pharmacological differences between bromocriptine and lisuride.

Bromocriptine	Lisuride
In normal mice	
No, or only very slight stereotyped behaviour	Strong stereotyped behaviour, dose-dependent
Hypothermia only after high doses	Hypothermia with very low doses
In reserpinised mice	
No stereotyped behaviour	Strong stereotyped behaviour at lower doses than in normal mice
Effects on motor activity and body temperature easily inhibited by very low doses of sulpiride	Stereotyped behaviour and effects on motor activity and body temperature virtually not affected by low or high doses of sulpiride
In reserpinised mice after additional pretreatment with α-methyl-p-tyrosine	
Effects on motor activity and body temperature completely abolished	No, or only very slight reduction of effects on motor activity and body temperature, and of stereotyped behaviour
In rats	
Strong and long-lasting prolactin-lowering effect with low doses	Strong and long-lasting prolactin-lowering effect with low doses
Slight behavioural effects (sniffing) only with high doses	Stereotyped behaviour
	Increased offensive-defensive postures with vocalisation and mounting behaviour, with doses as low as 0.1 mg/kg s.c., effects potentiated by MAO inhibitors and blocked by haloperidol, but not by sulpiride
	Increased group toxicity

aminergic and prolactin-lowering effects; however, there are also important pharmacological differences (table 1).

Our observation that effects of bromocriptine in mice could be inhibited by pretreatment with the tyrosine hydroxylase inhibitor α-methyl-p-tyrosine is in agreement with other reports from experiments with rats (Flückiger et al., 1976; Johnson et al., 1976). Similar effects of lisuride and apomorphine are not antagonized by this pretreatment and the prolactin-lowering effect of both compounds is also unaffected (Horowski and Gräf, 1976). However, the behavioural effects of lisuride in grouped rats (e.g. offensive-defensive behaviour, frequent mounting, increased group toxicity) seem to depend partly on the presence of endogenous dopamine, as these effects are strongly enhanced by pretreatment with the MAO-inhibitor nialamide. The frequent mounting behaviour induced by lisuride seems, nevertheless, to be due to the additional inhibition of serotonergic systems (Horowski and Wachtel, 1976; Da Prada et al., 1977) as this effect was not observed after treatment with apomorphine or bromocriptine under the same conditions.

This entire pharmacological pattern makes lisuride a very interesting drug for further pharmacological and clinical testing. As regards a potential anti-Parkinson effect of lisuride, its high potency on oral application in humans as well as its dopaminergic activity in both normal and, which may be more relevant, in supersensitive animals may be of great importance. This also applies to the possibility of using sulpiride to prevent side-effects, as suggested by our results, and finally, to the independence of its effects from the presence of endogenous dopamine.

In addition, it must be stressed that the pharmacological similarities between lisuride and d-LSD as reported here, as well as their biochemical similarities (Kehr, 1977; Kehr and Speckenbach, 1978) are striking. For this reason, the total absence of any hallucinogenic effect of lisuride in humans as revealed by our clinical experience indicates that further investigations of possible differences between these two drugs, e.g. their influence on dopaminergic and serotonergic balance in some brain regions, may be very helpful in elucidating the biological basis of hallucinations and related disorders in human disease.

Acknowledgements

I wish to thank SPOFA for the supply of d-LSD, and SANDOZ A.G. for the supply of bromocriptine and DELAGRANGE for the supply of sulpiride. For skilful technical assistance I thank Miss C. Riedel.

References

Boissier, J.R., A.J. Puech and P. Simon, 1977, Action of classic and unusual neuroleptics on various behavioural apomorphine-induced effects, in: Advances in Biochemical Psychopharmacology, Vol. 16, eds. E. Costa and G.L. Gessa (Raven Press, New York) p. 631.

Calne, D.B., P.F. Teychenne, L.E. Claveria, R. Eastman, J.K. Greenacre and A. Petrie, 1974, Bromocriptine in Parkinsonism, Brit. Med. J. 4, 442.

Carlsson, A., 1959, The occurence, distribution and physiological role of catecholamines in the central nervous system, Pharmacol. Rev. 11, 490.

Carlsson, A., 1972, Biochemical and pharmacological aspects of parkinsonism, Acta Neurol. Scand. 48, Suppl. 51, 11.

Carlsson, A., 1975, Receptor-mediated control of dopamine metabolism, in: Pre- and Postsynaptic Receptors, eds. E. Usdin and W.E. Bunney, Jr. (Marcel Dekker, New York) p. 49.

Carlsson, A., 1977, Dopaminergic autoreceptors: Backround and implications, in: Advances in Biochemical Psychopharmacology, Vol. 16, eds. E. Costa and G.L. Gessa (Raven Press, New York) p. 631.

Cools, R.A. and J.M. Van Rossum, 1976, Excitation-mediating and inhibition-mediating dopamine receptors: A new concept towards a better understanding of electrophysiological, biochemical, pharmacological, functional and clinical data, Psychopharmacologica (Berlin) 45, 243.

Corrodi, H., K. Fuxe, T. Hökfelt, P. Lidbrink and U. Ungerstedt, 1973, Effect of ergot drugs on central catecholamine neurons: Evidence for a stimulation of central dopamine neurons, J. Pharm. Pharmacol. 25, 409.

Corsini, G.U., M. del Zompo, C. Cianchetti and A. Mangoni, 1976, Therapeutical efficacy of a com-

bination of apomorphine with sulpiride or metoclopramide in parkinsonism, Psychopharmacol. 47, 169.

Di Chiara, G., L. Vargiu, M.L. Proceddu and G.L. Gessa, 1977, Bromocriptine: a rather specific stimulant of dopamine receptors regulating dopamine metabolism, in: Advances in Biochemical Psychopharmacology, Vol. 16, eds. E. Costa and G.L. Gessa (Raven Press, New York) p. 443.

Ehringer, R.H. and O. Hornykiewicz, 1960, Verteilung von Noradrenalin und Dopamin (3-hydroxytyramin) im Gehirn des Menschen und ihr Verhalten bei Krankheiten des extrapyramidalen Systems, Klin. Wschr. 38, 1236.

Flückiger, E., M. Marko, W. Doepfner and W. Niederer, 1976, Effects of ergot alkaloids on the hypothalamic-pituitary axis, Postgrad. Med. J. 52, Suppl. 1, 57.

Fuxe, K., L.F. Agnati, H. Corrodi, B.J. Everitt, T. Hökfelt, A. Löfström and U. Ungerstedt, 1975, Action of dopamine receptor agonists in forebrain and hypothalamus: Rotational behaviour, ovulation and dopamine turnover, in: Advances in Neurology, Vol. 9, eds. D. Calne, T.N. Chase and A. Barbeau (Raven Press, New York) p. 223.

Fuxe, K., L. Agnati, B.J. Everitt, T. Hökfelt, A. Ljungendahl and M. Perez de la Mora, 1977, Action of β(4-chlorphenyl)GABA, γ-hydroxybutyrolactone, and apomorphine on central dopamine neurons, in: Advances in Biochemical Psychopharmacology, Vol. 16, eds. E. Costa and G.L. Gessa (Raven Press, New York) p. 489.

Goldstein, M., R.L. Bronaugh, J.Y. Lew, T. Ohashi, G.S. Drummond and K. Fuxe, 1977, Effect of dopaminephilic agents and cAMP on tyrosine hydroxylase activity, in: Advances in Biochemical Psychopharmacology, Vol. 16, eds. E. Costa and G.L. Gessa (Raven Press, New York) p. 447.

Horowski, R. and K.-J. Gräf, 1976, Influence of dopaminergic agonists and antagonists on serum prolactin concentrations in the rat, Neuroendocrinol. 22, 273.

Horowski, R., F. Neumann and K.-J. Gräf, 1975, Influence of apomorphine hydrochloride, dibutyryl-apomorphine and Lysenyl on plasma prolactin concentrations in the rat, J. Pharm. Pharmacol. 27, 532.

Horowski, R. and H. Wachtel, 1976, Direct dopaminergic action of lisuride hydrogen maleate, an ergot derivative, in mice, European J. Pharmacol. 36, 373.

Horowski, R., H. Wendt and K.-J. Gräf, 1978, Prolactin-lowering effect of low doses of lisuride in man, Acta Endocrinol. (Kbh) 87, 234.

Johnson, A.M., D.M. Loew and J.M. Vigouret, 1976, Stimulant properties of bromocriptine on central dopamine receptors in comparison to apomorphine, (+)-amphetamine and L-DOPA, Brit. J. Pharmac. 56, 59.

Kehr, W., 1977, Effect of lisuride and other ergot derivatives on monoaminergic mechanisms in rat brain, European J. Pharmacol. 41, 261.

Kehr, W. and W. Speckbach, 1978, Effect of lisuride and LSD on monoamine synthesis after axotomy or reserpine treatment in rat brain, Naunyn-Schmiedeb. Arch. Pharmacol. 301, 163.

Da Prada, M., E.P. Bonetti and H.H. Keller, 1977, Induction of mounting behaviour in female and male rats by lisuride, Neurosci. Lett. 6, 349.

Puech, A.J., P. Simon and J.R. Boissier, 1976, Antagogism by sulpiride of three apomorphine-induced effects in rodents, European J. Pharmacol. 36, 439.

Spano, P.F., G. Di Chiara, P. Loddo, G.C. Tonon and M. Trabucchi, 1977, Dopamine-stimulated adenylate cyclase in rat substantia nigra: Localization and effects of neuroleptics, in: Advances in Biochemical Psychopharmacology, Vol. 16, eds. E. Costa, and G.L. Gessa (Raven Press, New York) p. 613.

Trabucchi, M., L. Longoni, P. Fresia and P.F. Spano, 1975, Sulpiride: a study of the effects on dopamine receptors in rat neostriatum and limbic forebrain, Life Sci. 17, 1551.

Trabucchi, M., P.F. Spano, G.C. Tonon and L. Frattola, 1976, Effects of bromocriptine on central dopaminergic neurons, Life Sci. 19, 225.

Vernier, V.G., H.M. Hanson and C.A. Stone, 1962, The pharmacodynamics of amitriptyline, in: Psychosomatic Medecine, eds. H.H. Nodine and J.H. Moyer (Lea and Febiger, Philadelphia) p. 683.