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DIRECT DOPAMINERGIC ACTION OF LISURIDE HYDROGEN MALEATE, AN ERGOT DERIVATIVE, IN MICE

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Lisuride hydrogen maleate induced stereotyped behaviour in normal as well as in reserpinized mice. It antagonized the motor depression and hypothermia induced by reserpine. On i.p. administration the compound was about as effective as apomorphine and D-amphetamine. As with apomorphine and in contrast to D-amphetamine the effects of lisuride hydrogen maleate in reserpinized mice were not impaired by additional treatment with α-methyl-p-tyrosine methylester. In untreated mice, the substance was very potent in lowering body temperature with significant hypothermia measured after dosages as low as 0.10 mg/kg i.p. Occurrence of stereotyped behaviour and hypothermia could be prevented by the dopaminergic antagonist haloperidol.

From these data it is concluded that lisuride hydrogen maleate in addition to its interaction with serotoninergic systems is a potent dopaminergic agonist with a probably direct action on dopaminergic receptors.

Further arguments in support of such an action of lisuride hydrogen maleate are, in addition to biochemical data, its serum prolactin lowering effect in rats, its strong emetic action in dogs and its effects on rat behaviour.

Lisuride hydrogen maleate Ergot derivatives Dopaminergic agonists

1. Introduction

Lisuride hydrogen maleate (Lysenyl® Spofa, N-(D-6-methyl-8-isoergolenyl)-N′,N′-diethylcarbamide hydrogen maleate, see fig. 1), is a derivative of isolysergic acid with strong peripheral antiserotonin activity (Votava and Lamplová, 1961). This compound was synthesized by Zikan and Semonský (1960) and is used mainly as a prophylactic agent in migraine.

In preliminary studies in mice we observed that lisuride hydrogen maleate produced stereotyped behaviour (Horowski et al., 1975). Stereotyped behaviour can be induced by apomorphine and D-amphetamine in rodents where it is regarded as a specific expression of the stimulation of the nigro-neostriatal dopaminergic systems (for review see Randrup and Munkvad, 1968). This action was hitherto unknown for lisuride hydrogen maleate. From electrophysiological studies in healthy volunteers it has been reported that lisuride hydrogen maleate at very low doses led to an EEG pattern which had some similarities to the effects seen after D-amphetamine and to a lesser degree after diazepam as demonstrated by computer EEG profiles (Itil et al., 1975).

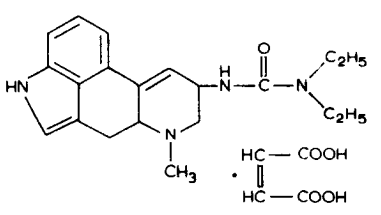

Fig. 1. Structure of lisuride hydrogen maleate.

A central dopaminergic action has been postulated for several other ergot derivatives such as ergocornine and 2-bromo-α-ergocryptine (Hökfelt and Fuxe, 1972; Corrodi et al.,

1973), α-ergocryptine, β-ergocryptine, ergocristine (Johnson et al., 1973) and ergometrine (Woodruff et al., 1974). 2-Bromo-α-ergocryptine, a compound which is known to lower prolactin levels (Flückiger, 1972) also induces stereotyped behaviour and antagonizes the motor depression induced by reserpine in the rat (Johnson et al., 1974). In animals with chronic unilateral degeneration of nigro-neostriatal and mesolimbic dopaminergic neurons caused by 6-hydroxydopamine, d-LSD also produced symptoms which were interpreted as an activation of supersensitive dopaminergic receptors (Fuxe et al., 1975).

We were therefore interested in investigating lisuride hydrogen maleate with regard to a potential dopaminergic action in comparison with apomorphine, a direct dopaminergic agonist, and D-amphetamine which is thought to act by releasing dopamine and noradrenaline from extragranular neuronal stores (for review see Carlsson, 1972).

2. Materials and methods

2.1. Drugs and solutions

The following drugs were used: lisuride hydrogen maleate (Spofa, Prague), D-amphetamine sulphate (Merck, Darmstadt), apomorphine hydrochloride (Sandoz AG, Basle), methysergide bimaleate (Sandoz AG, Basle), D-lysergic acid diethylamide (d-LSD, Sandoz AG, Basle), reserpine hydrochloride (Boehringer, Mannheim), α-methyl-p-tyrosine methylester hydrochloride (H 44/68 Hässle AB, Gothenburg) and haloperidol (Janssen AG, Düsseldorf).

Most substances were dissolved in 0.9% saline. Reserpine hydrochloride was suspended in a solution of 0.085% Myrj 53 (polyoxyethylenestearate, Atlas-Chemie, Essen) in 0.9% saline with the help of a RHEWUM L sonifier to achieve a fine distribution. Methysergide was suspended in the same way except that a 5% solution of Cremofor EL (BASF, Ludwigshafen) was used instead of Myrj 53.

2.2. Administration

If not stated otherwise, the solutions and suspensions were administered by i.p. injection with randomized allocation of treatment. The controls were given the corresponding vehicle. All doses were calculated as base and administered in a volume of 0.2 ml per 20 g body weight.

2.3. Animals

NMRI mice of both sexes weighing 18—25 g (Dr. Schwarz, Schering AG, Berlin) were used. The animals received a standard diet and water ad libitum. For p.o. testing the animals were given a 20% sucrose solution ad libitum 24 hr before the beginning of the experiment only. 1 hr before testing the animals were placed into individual acrylic glass cages (9 × 10 × 9 cm) in a diffusely illuminated room maintained at a temperature of 22 ± 1°C and constant humidity. Except for time—effect studies, all testing was performed between 9 and 11 a.m.

2.4. Test methods

In some experiments, animals were pretreated with reserpine (4 mg/kg i.v., 22—24 hr) alone or in combination with α-methyl-p-tyrosine methylester (400 mg/kg i.p., 3.5 hr), or with haloperidol (0.10, 0.39 and 1.56 mg/kg i.p., 60 or 120 min).

Animals were observed in their individual cages for 1 min for the evaluation of stereotyped behaviour by an experienced observer who was not aware of the treatment of the animals. In animals which displayed chewing, licking or gnawing movements for more than 30 sec within this period the symptom stereotyped behaviour was taken to be present. These observations were performed at 30, 60, 120 or 240 min after injection as indicated under Results.

The motor activation in animals whose spontaneous motor activity had been abolished by pretreatment with reserpine alone or in combination with α-methyl-p-tyrosine methylester was evaluated by the method of Vernier et al. (1962) with minor modifications. Animals were exposed to an open field (60 × 45 × 7 cm) and scored positive for motor activity on covering a minimum distance of 20 cm within 1 min. Thus, for a positive score no complete restoration of motor activity was required, but merely a minimal motor response 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).

2.5. Statistics

Statistical significance was evaluated using the Mann and Whitney U-test (Mann and Whitney, 1947). Median effective doses (ED_{50}) and 95% confidence limits were determined by probit analysis (Finney, 1952).

3. Results

3.1. Stereotyped behaviour and motor activity

3.1.1. Normal mice

In mice which had been given no previous treatment lisuride hydrogen maleate induced stereotyped behaviour as shown in table 1, the compound being 3—4 times more potent on i.p. than on p.o. administration. Stereotyped behaviour, induced by lisuride hydrogen maleate, seemed to be somewhat less pronounced and striking than that seen after apomorphine or D-amphetamine treatment.

3.1.2. Mice treated with catecholamine-depleting agents

Mice were pretreated with an i.v. injection of 4 mg/kg reserpine, a known depletor of catecholamines and serotonin (Carlsson, 1966). In these animals, which had lost all spontaneous activities the stereotyped behaviour caused by lisuride hydrogen maleate could be detected very easily. The animals were about 5 times more sensitive to lisuride hydrogen maleate than were untreated mice (table 1). This ratio was not affected by additional pretreatment with the tyrosine hydroxylase inhibitor α-methyl-p-tyrosine methylester, which had been given in order to eliminate the reserpine-resistant pool of newly synthesized catecholamines (Hanson, 1967).

Like apomorphine, lisuride hydrogen maleate antagonized the motor depression produced by reserpine. Neither of the compounds could restore the motor activity of the mice completely. The movements induced consisted mainly of monotonous uncoordinated walking as described by Andén et al. (1973). Also, the effect on motor activity was not altered by additional treatment with α-methyl-p-tyrosine methylester.

In this respect lisuride hydrogen maleate was as potent as apomorphine and D-amphetamine in inducing stereotyped behaviour and restoring motor activity in reserpinized mice. D-amphetamine, however, was at least 10 times less potent after additional treatment with α-methyl-p-tyrosine methylester, whilst apomorphine behaved like lisuride hydrogen maleate. After oral administration in reserpine-pretreated mice, lisuride hydrogen maleate was as potent as D-amphetamine whereas the ED_{50} of apomorphine was clearly higher, an effect which is in agreement with the known low oral activity of this drug.

The action of lisuride hydrogen maleate in animals pretreated with reserpine lasted only 30 min. The same applies to apomorphine while the effect of D-amphetamine, especially in higher dosages, appeared to last a little longer (table 2).

In an attempt to see whether the anti-reserpine effect of lisuride hydrogen maleate could also be observed with other ergot derivatives possessing high anti-serotonin activities at peripheral organs, d-LSD and methysergide

TABLE 1

Induction of stereotyped behaviour and motor activation by lisuride hydrogen maleate, D-amphetamine and apomorphine in mice pretreated with reserpine alone or in combination with α-methyl-p-tyrosine.

Values indicate ED_{50} (mg/kg) with 95% confidence limits at 30 min after administration.

Treatment	Pretreatment Stereotyped behaviour	Reserpine (4 mg/kg i.v. 22 hr)		Reserpine (4 mg/kg i.v. 22 hr) + α-methyl-p-tyrosine (400 mg/kg 3.5 hr)	
		Stereotyped behaviour	Motor activity	Stereotyped behaviour	Motor activity
Lisuride hydrogen maleate i.p.	1.50 (1.01—2.51)	0.30 (0.18—0.41)	0.23 (0.04—0.40)	0.25 (0.19—0.31)	0.24 (0.08—0.34)
D-amphetamine i.p.		0.63 (0.47—0.79)	0.25 (0.13—0.44)	>3.13	>3.13
Apomorphine i.p.		0.57 (0.44—0.72)	0.37 (0.10—0.46)	0.21 (0.13—0.30)	0.16 (0.10—0.24)
Lisuride hydrogen maleate p.o.	5.82 (2.60—8.16)	0.84 (0.48—1.50)	0.22 (0.06—0.44)		
D-Amphetamine p.o.		0.89 (0.57—1.57)	0.69 (0.44—1.17)		
Apomorphine p.o.		2.73 (1.86—4.13)	1.40 (0.77—2.22)		

were tested under the same conditions (table 3). From this preliminary experiment it turned out that 10 and 50 mg/kg d-LSD in reserpinized mice could also induce stereotyped behaviour and restore motor activity. At the higher dose level violent tremors were observed which interfered with the observation of stereotyped behaviour. After methysergide treatment, too, some reserpine antagonistic effects could be detected, specially after the high dosage of 100 mg/kg i.p. 4 hr post injection.

TABLE 2

Time course of the effects of lisuride hydrogen maleate, D-amphetamine and apomorphine in mice pretreated with reserpine (4 mg/kg i.v., 22 hr).

Values indicate number of animals displaying stereotyped behaviour and motor activation.

Treatment	30 min		60 min		120 min		240 min	
	Stereotyped behaviour	Motor activity	Stereotyped behaviour	Motor activity	Stereotyped behaviour	Motor activity	Stereotyped behaviour	Motor activity
0.9% Saline (i.p.)	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10
Lisuride hydrogen maleate (0.78 mg/kg i.p.)	10/10	8/10	3/10	5/10	1/10	3/10	0/10	0/10
D-amphetamine (0.78 mg/kg i.p.)	5/10	7/10	0/10	4/10	0/10	1/10	0/10	0/10
Apomorphine (0.78 mg/kg i.p.)	9/10	10/10	2/10	4/10	1/10	0/10	0/10	0/10
Lisuride hydrogen maleate (3.13 mg/kg i.p.)	10/10	8/10	3/10	5/10	1/10	3/10	0/10	0/10
D-Amphetamine (3.13 mg/kg i.p.)	10/10	10/10	8/10	10/10	1/10	8/10	1/10	0/10
Apomorphine (3.13 mg/kg i.p.)	10/10	10/10	5/10	7/10	0/10	0/10	0/10	0/10

TABLE 3

Time course of the effects of lisuride hydrogen maleate, LSD and methysergide in mice pretreated with reserpine (4 mg/kg i.v., 22 hr).

Values indicate number of animals displaying stereotyped behaviour and motor activation.

Treatment	30 min		60 min		120 min		240 min	
	Stereotyped behaviour	Motor activity	Stereotyped behaviour	Motor activity	Stereotyped behaviour	Motor activity	Stereotyped behaviour	Motor activity
0.9% Saline (i.p.)	0/20	4/20	0/20	0/20	0/20	0/20	0/20	2/20
Lisuride hydrogen maleate (1.0 mg/kg i.p.)	18/20	9/20	14/20	9/20	1/20	7/20	0/20	0/20
Lisuride hydrogen maleate (10 mg/kg i.p.)	19/20	19/20	17/20	15/20	11/20	15/20	0/20	6/20
LSD (10 mg/kg i.p.)	10/10	7/10	8/10	8/10	8/10	10/10	2/10	3/10
LSD (50 mg/kg i.p.)	4/10 *	8/10	4/10 *	8/10	8/10 *	10/10	10/10	9/10
5% Cremofor EL (i.p.)	0/20	5/20	0/20	3/20	0/20	1/20	1/20	3/20
Methysergide (10 mg/kg i.p.)	2/20	5/20	3/20	9/20	1/20	13/20	2/20	10/20
Methysergide (100 mg/kg i.p.)	0/20	8/20	0/20	6/20	2/20	5/20	13/20	12/20

* Animals had violent tremor interfering with observation of stereotyped behaviour.

3.1.3. Mice pretreated with haloperidol

Table 4 shows the influence of pretreatment with haloperidol, a drug which is thought to act by blocking catecholamine receptors (Carlsson and Lindqvist, 1963; Van Rossum, 1967). As can be seen, haloperidol in a dose of 1.56 mg/kg i.p. given 60 min before testing abolished the stereotyped behaviour induced by 6.25 mg/kg lisuride hydrogen maleate. The dose of 0.10 mg/kg haloperidol had no effect.

TABLE 4

Influence of pretreatment with haloperidol on stereotyped behaviour induced by lisuride hydrogen maleate.

Values indicate number of animals displaying stereotyped behaviour.

Pretreatment	Treatment Lisuride hydrogen maleate (6.25 mg/kg i.p., 30 min)
0.9% Saline (i.p., 60 min)	10/10
Haloperidol (0.1 mg/kg i.p., 60 min)	10/10
Haloperidol (0.39 mg/kg i.p., 60 min)	9/10
Haloperidol (1.56 mg/kg i.p., 60 min)	1/10

3.2. Body temperature

The investigation of the influence of lisuride hydrogen maleate on the regulation of body temperature in mice produced a very complex picture depending on the state of the animals (table 5).

3.2.1. Normal mice

In normal mice, there was a significant drop in body temperature after i.p. injection of 0.1, 0.39 and 1.56 mg/kg lisuride hydrogen maleate. After the highest dose, body temperature was about 3°C lower than in control

TABLE 5

Influence of lisuride hydrogen maleate, D-amphetamine and apomorphine on body temperature of untreated mice and mice pretreated with reserpine alone or in combination with α-methyl-p-tyrosine.

Body temperature is expressed in °C as mean ± S.E.M. All values were obtained with a rectal thermometer at 30 min after i.p. administration of drugs.
Number of animals in parentheses

Treatment	Pretreatment	Reserpine (4 mg/kg i.v., 22 hr)	Reserpine (4 mg/kg i.v., 22 hr) + α-methyl-p-tyrosine (400 mg/kg i.p. 3.5 hr)
Controls (0.9% saline)	36.4 ± 0.2 (10)	30.9 ± 0.3 (10)	25.0 ± 0.3 (10)
Lisuride hydrogen maleate (mg/kg, i.p.)			
0.10	34.0 ± 0.3 ** (10)	31.9 ± 0.7 (7)	
0.20		33.2 ± 0.6 ** (7)	
0.39	33.8 ± 0.3 ** (10)	33.2 ± 0.7 ** (7)	
0.78		33.7 ± 0.8 ** (7)	26.3 ± 0.4 ** (10)
1.56	33.5 ± 0.3 ** (10)	34.7 ± 0.8 ** (7)	
3.13			26.9 ± 0.2 ** (10)
D-amphetamine (mg/kg, i.p.)			
0.10		31.7 ± 0.6 (7)	
0.20		32.7 ± 0.5 ** (7)	
0.39	35.9 ± 0.4 (10)	33.7 ± 0.3 ** (7)	
0.78		33.7 ± 0.4 ** (7)	26.9 ± 0.6 ** (10)
1.56	36.8 ± 0.2 (10)	35.2 ± 0.7 ** (7)	
3.13			27.0 ± 0.4 ** (10)
Apomorphine (mg/kg, i.p.)			
0.10			
0.20		32.4 ± 0.3 * (7)	
0.39	36.3 ± 0.3 (10)	32.9 ± 0.6 ** (7)	
0.78		34.9 ± 0.5 ** (7)	27.9 ± 0.3 ** (10)
1.56	35.1 ± 0.3 ** (10)	37.0 ± 0.5 ** (7)	
3.13		37.4 ± 0.5 ** (7)	29.1 ± 0.5 ** (10)

* Difference from control $p \leq 0.05$ (U-test).
** Difference from control $p \leq 0.01$ (U-test).

animals. Apomorphine produced significant hypothermia only at a dose of 1.56 mg/kg i.p., whereas 0.39 mg/kg i.p. as well as D-amphetamine at the same dose level were without a significant effect. After 1.56 mg/kg D-amphetamine i.p., body temperature appeared to be higher than in controls, a tendency which, however, did not reach statistical significance.

The effect of lisuride hydrogen maleate on body temperature 30 min after injection was dose dependent with dosage groups as low as 0.10 mg/kg i.p., differing significantly from controls ($p \leq 0.05$, see fig. 2). 2 hr after injec-

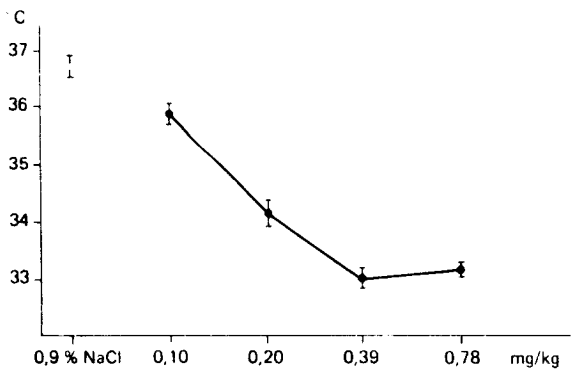

Fig. 2. Influence of lisuride hydrogen maleate on body temperature in mice (mean ± S.E.M.). Mice were treated with lisuride hydrogen maleate given i.p. Body temperature was recorded with a rectal probe 30 min after injection.

tion the body temperature of animals treated with doses up to 0.78 mg/kg i.p. had returned to normal values (data not shown).

3.2.2. Mice treated with catecholamine-depleting agents

All three agents antagonized the drop in body temperature produced by reserpine in a comparable dose range (table 5). When the animals had been pretreated additionally with α-methyl-p-tyrosine methylester, the antagonistic effect of lisuride hydrogen maleate as well as of apomorphine and D-amphetamine could not be abolished. Apomorphine was the most active compound in these animals, but D-amphetamine also elevated the body temperature significantly.

3.2.3. Mice pretreated with haloperidol

Haloperidol at a dose level which by itself did not cause significant hypothermia counteracted the drop in body temperature produced by lisuride hydrogen maleate as well as by apomorphine (see table 6).

4. Discussion

Our results show that lisuride hydrogen maleate induced stereotyped behaviour in mice. This effect can be considered a sign of the activation of nigro-neostriatal dopaminergic receptors as has been suggested on the basis of experiments using the dopaminergic agonists apomorphine and D-amphetamine

TABLE 6

Influence of pretreatment with haloperidol on hypothermia induced by lisuride hydrogen maleate and apomorphine.
Body temperature is expressed in °C as mean ± S.E.M.
Number of animals in parentheses.

Treatment	0.9% Saline (i.p., 120 min)	Haloperidol (1.56 mg/kg i.p., 120 min)
0.9% Saline (i.p., 30 min)	36.9 ± 0.2 (10)	36.3 ± 0.3 (10)
Lisuride hydrogen maleate (0.39 mg/kg i.p., 30 min)	35.6 ± 0.2 (10)	37.1 ± 0.2 (10) **
Lisuride hydrogen maleate (1.56 mg/kg i.p., 30 min)	34.3 ± 0.5 (10)	35.7 ± 0.2 (10) *
Apomorphine (1.56 mg/kg i.p., 30 min)	34.4 ± 0.2 (10)	36.5 ± 0.3 (10) **
Apomorphine (6.25 mg/kg i.p., 30 min)	33.5 ± 0.4 (8)	35.5 ± 0.6 (8) **

* Difference from control $p \leq 0.05$ (U-test).
** Difference from control $p \leq 0.01$ (U-test).

(for review see Carlsson, 1972). The stereotyped behaviour induced by lisuride hydrogen maleate could be blocked by pretreatment with the neuroleptic haloperidol, an effect which has been known for a long time in the case of apomorphine and D-amphetamine (Janssen et al., 1960, 1965). In reserpine-pretreated mice, lisuride hydrogen maleate was about 5 times more effective than in untreated animals. It has been proposed that a drop in the endogeneous dopamine levels induced by reserpine leads to receptor supersensitivity which may increase the effectiveness of dopaminergic agonists (Fuxe et al., 1970). This could possibly explain the higher activity of lisuride hydrogen maleate in these animals.

Further, lisuride hydrogen maleate antagonized the immobility caused by reserpine. The reserpine-induced motor depression seems to be due mainly to a central dopamine deficiency; accordingly, the immobility of the test animals can be antagonized to a large extent by dopaminergic agonists while complete restoration of motility appears to require the additional activation of central noradrenergic receptors (Andén et al., 1970, 1973). In this respect, lisuride hydrogen maleate and apomorphine differed from D-amphetamine which fully restored the spontaneous activity of mice treated with reserpine.

Both lisuride hydrogen maleate and apomorphine produced a significant fall in body temperature whereas D-amphetamine had no significant effect at 0.39 and 1.56 mg/kg i.p. In the case of apomorphine, this hypothermic effect is thought to be another result of central dopamine receptor stimulation (Fuxe et al., 1970). This effect can be antagonized by the dopaminergic antagonist haloperidol, but not by the α-adrenolytic compound phentolamine (Barnett et al., 1972). In agreement with this, the hypothermic effect of lisuride hydrogen maleate could also be blocked by haloperidol. In reserpinized mice, lisuride hydrogen maleate increased the low body temperature. The same effect was observed after apomorphine and D-amphetamine treatment.

All these results strongly support the hypothesis that lisuride hydrogen maleate has central dopaminergic activity. As regards the possible mechanism of this action, it can be assumed that this compound acts directly on dopamine receptors as its effects were not prevented by the combined pretreatment with reserpine and α-methyl-p-tyrosine methylester. In this respect lisuride hydrogen maleate is similar to apomorphine whose effects are not antagonized by inhibition of catecholamine synthesis with α-methyl-p-tyrosine methylester as is the case with D-amphetamine (Ernst, 1967; Andén et al., 1967). Our results obtained in mice confirm this difference between apomorphine and D-amphetamine with the only exception of body temperature where D-amphetamine is also still effective. This result could, however, be due to the complex effects of D-amphetamine on mechanisms regulating body temperature (Yehuda and Wurtman, 1972).

As in the case of stereotyped behaviour, lisuride hydrogen maleate, apomorphine and D-amphetamine appear to be about equally effective after i.p. application as antagonists of reserpine-induced motor depression and hypothermia. On the other hand, in mice which are not pretreated with reserpine, the high potency of lisuride hydrogen maleate in lowering the body temperature is striking. A conceivable explanation of this result could be that other properties of lisuride hydrogen maleate such as its influence on serotoninergic systems (Votáva and Lamplová, 1961) may have a synergistic effect. It is noteworthy in this context that the hypothermia observed in rats after low doses of D-amphetamine could be intensified by methysergide (Yehuda and Wurtman, 1972). The predominating effect of dopaminergic systems is, however, supported by the blocking effect of haloperidol.

It is remarkable that apomorphine and lisuride hydrogen maleate, which antagonize the fall in body temperature caused by reserpine, are able to produce hypothermia in untreated animals. Moreover this effect can be prevented by haloperidol, which itself lowers

body temperature at higher dosages (unpublished results). Therefore, it appears that compounds which inter alia inhibit dopaminergic neurotransmission produce the same effect as dopaminergic agonists. There is, however, one difference which may be significant: agents which inhibit catecholaminergic neurotransmission, such as reserpine, α-methyl-p-tyrosine methylester or neuroleptics, seem to cause some breakdown of thermoregulation as indicated by a very pronounced and dramatic fall of body temperature in mice maintained at room temperature.

This effect might possibly be correlated with the general depressant effect of these dopaminergic antagonists (Lomax, 1970). In contrast, the hypothermia produced in our experiments by apomorphine and lisuride hydrogen maleate tends to be mild even at high dose levels and may perhaps be interpreted as resulting from an activation of a physiological thermoregulatory process. Whilst in this case animals merely seem to maintain their body temperature at a slightly different level, animals treated with neuroleptics appear to have lost their thermoregulation altogether. As a consequence, their body temperature falls passively almost to the temperature of their environment.

Further actions of lisuride hydrogen maleate which are consistent with the hypothesis of a central dopaminergic mechanism of this drug, as it is known for apomorphine, are summarized in table 7. Both compounds can induce aggressive behaviour as demonstrated by offensive—defensive postures. In addition, lisuride hydrogen maleate at dosages as low as 0.1 mg/kg s.c. has a very strong serum prolactin lowering effect in rats (Horowski et al., 1975), and also has a strong emetic effect in dogs at 0.01 mg/kg s.c. (Podvalová et al., unpublished results), where it is at least as active as apomorphine, for which an emetic ED_{50} of 0.03 mg/kg s.c. has been reported (Niemegeers, 1974).

Other effects of lisuride hydrogen maleate, such as the increased mounting behaviour produced by this compound in rats (Podvalová and Dlabač, 1970; Benkert and Eversmann, 1972), possibly involve an inhibition of serotoninergic systems combined with catecholaminergic activation as has been proposed for this kind of behaviour (Tagliamonte et al., 1969). Furthermore, stereotyped behaviour could also be observed in rats, but to a less pronounced extent than in mice (own unpublished observations). A dopaminergic action of lisuride hydrogen maleate is also in agreement with the biochemical findings. In rats, Dlabač (cf. Podvalová et al., unpublished results) reported a marked increase in brain dopamine levels following an intravenous in-

TABLE 7

Some pharmacological similarities between lisuride hydrogen maleate and apomorphine.

Effect	Species	Lisuride hydrogen maleate	Apomorphine
Induction of stereotyped behaviour	Mice	(Own results)	(Randrup and Munkvad, 1968)
Antagonism of reserpine-induced motor depression	Mice	(Own results)	(Andén et al., 1970)
Hypothermia	Mice	(Own results)	(Fuxe et al., 1970)
Aggressive behaviour	Rat	(Podvalová and Dlabač, 1970)	(McKenzie, 1971; Dlabač, 1973)
Decrease of serum prolactin	Rat	(Horowski et al., 1975)	(Smalstig and Sawyer, 1974)
Emesis	Dog	(Podvalová et al., 1970)	(Niemegeers, 1974)

jection of 0.3 mg/kg lisuride hydrogen maleate. These results were confirmed (Kehr et al., unpublished results) and it was further shown that lisuride hydrogen maleate lowered the synthesis rate of dopamine, an effect which is also known for apomorphine (Kehr et al., 1975).

All these considerations further support the hypothesis that lisuride hydrogen maleate is a potent central dopaminergic agonist in addition to being a serotonin antagonist in peripheral organs. There is no direct correlation between these two properties as is indicated by the lower activity of d-LSD and especially methysergide with respect to reserpine antagonism, whereas the same compounds are more potent than lisuride hydrogen maleate with respect to peripheral serotonin antagonism (Votáva and Lamplová, 1961). Dopaminergic activity has also been described (for review see Fuxe et al., 1975) for other ergot derivatives. This is apparently independent of the well-known effects of ergot drugs on noradrenergic and serotoninergic mechanisms as well as of their direct action on smooth muscles of blood vessels and uterus. Therefore, it is tempting to speculate that some of the so-called central actions of ergot alkaloids (Rothlin, 1947), such as emesis, hypotension or hypothermia, can, at least in part, be interpreted as an expression of a dopaminergic action.

The combination of peripheral serotonin antagonism and dopaminergic agonist activity as predominant effects in animals makes lisuride hydrogen maleate an interesting compound for clinical studies. In its anti-serotonin effect it is quite similar to methysergide, which in humans is mainly used as a prophylactic agent in migraine therapy (Curran et al., 1967). As a dopaminergic agonist it can be compared with 2-bromo-α-ergocryptine whose prolactin lowering effect is well known (Flückiger, 1972) but which has recently also been reported to be an effective anti-parkinson agent (Claveria et al., 1975). An anti-migraine effect of lisuride hydrogen maleate seems to be likely, as indicated by clinical trials against methysergide (Herrmann et al., in preparation); the clinical significance of a possible dopaminergic action of lisuride hydrogen maleate, however, remains to be investigated.

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