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Effect of Lisuride and LSD on Monoamine Synthesis after Axotomy or Reserpine Treatment in Rat Brain*

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Summary. The effect of d-lysergic acid diethylamide (LSD) and lisuride on the synthesis of monoamines was evaluated in rat brain regions using an in vivo method in which the accumulation of dopa and 5-hydroxytryptophan (5-HTP) is measured after inhibition of the aromatic amino acid decarboxylase by means of 3-hydroxybenzylhydrazine.

LSD (50–1000 µg/kg i.p.) caused a dose-dependent increase in dopa formation and a slight elevation of tyrosine and tryptophan concentrations in the intact rat forebrain; moreover, it reduced the accumulation of 5-HTP.

The increase in dopa formation in the terminal system of the rat forebrain following an axotomy of the ascending monoaminergic fiber system was antagonized by LSD at a dose of 0.5 mg/kg i.p. Haloperidol (2 mg/kg i.p.) counteracted the effect of LSD.

The increase in dopa formation in c. striatum and the dopamine-rich part of the limbic system following treatment with reserpine was antagonized by lisuride as well as by LSD. However, lisuride was at least 10 times as potent as LSD. In reserpinized animals LSD counteracted the inhibitory effect on dopa accumulation of the direct dopamine receptor stimulant apomorphine while lisuride did not. The data suggest that LSD is a weak agonist at dopamine receptors in vivo with partial receptor blocking properties at higher doses, while the action of lisuride on dopamine receptors is a potent, purely agonistic one.

Key words: Dopamine receptors – Striatum – LSD – Lisuride – Reserpine – Monoamine synthesis.

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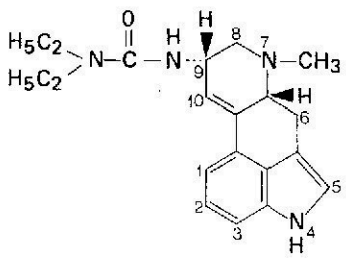
INTRODUCTION

In recent years a number of ergot derivatives has been reported to interact with monoaminergic receptors in the central nervous system. Among these are lisuride and d-lysergic acid diethylamide (LSD). These two compounds are similar in structure (Fig. 1), yet, in contrast to LSD lisuride is apparently not psychotomimetic in man.

Comparison of the available neuropharmacological data reveals some striking similarities between the

Lisuride



Lysergic acid diethylamide

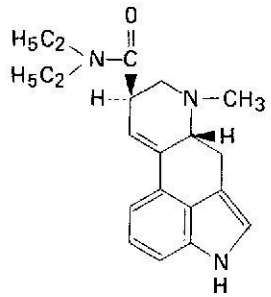


Fig. 1. Chemical structure of lisuride and lysergic acid diethylamide

actions of the two compounds. LSD has been shown to inhibit the electrical activity of 5-hydroxytryptamine (5-HT) containing neurons (Aghajanian et al., 1968; Andén et al., 1968; Carlsson and Lindqvist, 1972) which was interpreted as a receptor-mediated feedback inhibition due to the 5-HT receptor stimulating properties of LSD. Lisuride causes very similar changes in 5-HT neurons e.g. a reduction in the synthesis and metabolism of 5-HT (Kehr, 1977a; Keller et al., 1977).

In addition, LSD was shown to act as a dopamine agonist in vitro (von Hungen et al., 1975; Da Prada et al., 1975; Spano et al., 1975) as well as in vivo (Pieri et al., 1974; Kelly and Iversen, 1975). Since lisuride was also shown to be a dopamine agonist in vivo (Horowski and Wachtel, 1976) we compared the two structural congeners with regard to their ability to interfere with dopamine and 5-HT receptor-mediated feedback mechanisms in rat brain in vivo (Kehr, 1977a). As an extension of the latter investigation the effect of LSD and lisuride on monoamine synthesis was compared after axotomy of the ascending monoaminergic fiber system and after pretreatment with reserpine.

MATERIAL AND METHODS

Male Wistar rats weighing 180–220 g (Dept. Tierzucht und -haltung, Schering AG, Berlin) were used. The animals received a standard diet (Herilan®) and water ad libitum. Before each experiment the animals were divided at random into the various treatment groups. The following drugs were used: Reserpine hydrochloride (Serpasil®, Ciba/Geigy, Basel, Switzerland), lisuride hydrogen maleate (Cuvalit®, Spofa, Prague, Czechoslovakia), (+)-lysergic acid diethylamide tartrate (d-LSD, Sandoz AG, Basel, Switzerland), apomorphine hydrochloride (Sandoz AG, Basel, Switzerland), haloperidol (Janssen, Düsseldorf, Germany), 3-hydroxybenzylhydrazine hydrochloride (NSD 1015, Sandev Ltd., Harlow/Essex, England). Haloperidol was dissolved in a few drops of acetic acid and the final volume was made up with 5.5% glucose solution. All other drugs were dissolved in 0.9% saline solution. All solutions were administered i.p. The control animals were injected with the corresponding vehicles. The dose of NSD 1015 refers to the salt, the doses of all other compounds refer to the respective base. All compounds were injected in a volume of 5 ml/kg bodyweight.

Axotomy of the ascending monoaminergic fibers was performed by means of a complete transverse cerebral hemisection under light ether anaesthesia at the level of the caudal hypothalamus as described by Bédard et al. (1972). In sham operated animals a transverse slot was drilled at the middle between lambda and bregma, and the dura mater was split.

The accumulation of dopa and 5-hydroxytryptophan (5-HTP) 30 min after injection of the aromatic amino acid decarboxylase inhibitor NSD 1015 (100 mg/kg i.p.), was used to measure the rate-limiting steps in the synthesis of catecholamines and 5-HT in rat brain (Carlsson et al., 1972). The rats were killed by decapitation and the brains were quickly taken out. In some experiments the brains were dissected on an ice-cold plate according to Carlsson and Lindqvist (1973). The following parts of the brain were taken for analysis:

1. The corpus striatum, 2. the dopamine-rich part of the limbic system containing e.g. the olfactory tubercle, nucleus accumbens (medial part), and nucleus amygdaloideus centralis; and 3. the rest of the cortex (frontal, part of the temporal, parietal and occipital cortex referred to as neocortex).

Immediately after dissection the brain parts were frozen on dry ice and stored at −70° C until analysis (max. 2 weeks).

The brain parts from 2 animals were pooled and extracted with 10.3 ml ice-cold 0.4 N perchloric acid containing 5 mg $Na_2S_2O_5$ and 20 mg EDTA.

The extracts were purified on a strong cation exchange column (Dowex 50, X-4) (Atack and Magnusson, 1970; Kehr et al., 1972).

The following spectrophotofluorimetric analyses were performed: tyrosine (Waalkes and Udenfriend, 1957), dopa (Kehr et al., 1972), tryptophan (Bédard et al., 1972), 5-hydroxytryptophan (Atack and Lindqvist, 1973).

Statistics. One-way analysis of variance was applied and the means were compared by Dunnett-test or Scheffé-test.

RESULTS

Effect of LSD on Tyrosine and Tryptophan Hydroxylation

After inhibition of the aromatic amino acid decarboxylase with NSD 1015 (100 mg/kg i.p.) LSD in doses of 200–1000 µg/kg i.p., given 5 min prior to NSD 1015 led to a dose-dependent increase in the accumulation of dopa in the rat forebrain (Fig. 2a). After 1 mg/kg of LSD dopa formation was increased by more than 100%. Tyrosine was increased in the same dose range.

In contrast, the formation of 5-HTP was reduced in rat forebrain already at a dose of 50 µg/kg i.p., a minimum of 70% of the control level being reached at a dose of 200 µg/kg (Fig. 2b). Tryptophan levels were increased by about 30% after all doses of LSD tested (Fig. 2b).

Effect of LSD on Tyrosine and Tryptophan Hydroxylation after Axotomy

Axotomy of the ascending monoaminergic fibers by means of a cerebral hemitranssection caused an increase in tyrosine hydroxylation of 150% during 30 min after decarboxylase inhibition with NSD 1015 (100 mg/kg i.p.) as compared to the intact forebrain or sham operated controls (Fig. 3a). The low dose of LSD of 0.05 mg/kg neither changed dopa formation in the intact nor in the lesioned forebrain. A dose of 0.5 mg/kg left the accumulation unchanged on the intact side but reduced the increase in dopa induced by the lesion by 28%. Haloperidol (2 mg/kg i.p.) 30 min prior to hemisection counteracted the effect of LSD completely on the lesioned side and increased tyrosine hydroxylation on the intact side by more than 100% as compared to hemisection controls.

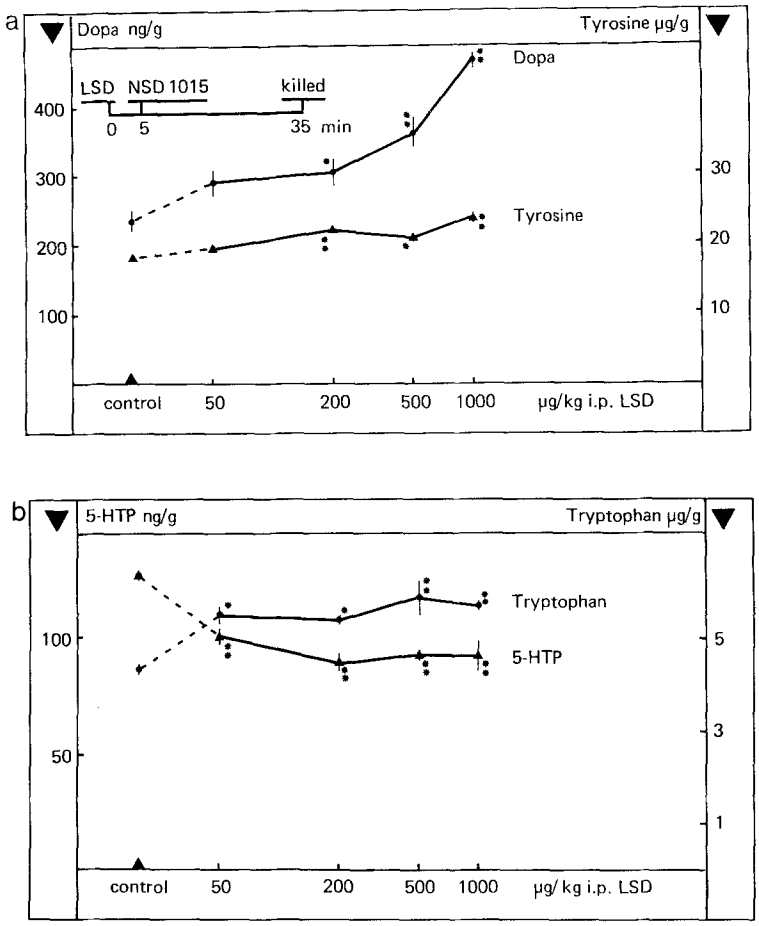


Fig. 2
Effect of various doses of LSD on tyrosine hydroxylation (a) and tryptophan hydroxylation (b) in rat forebrain. LSD was given i.p. 5 min prior to NSD 1015, 100 mg/kg i.p., and the animals were decapitated after another 30 min. Shown are the means ± S.E.M., $N = 6$. Statistics: One-way analysis of variance, Dunnett-test. Stars indicate significant differences from control values * $P < 0.05$, ** $P < 0.01$

As shown in earlier investigations (Speckenbach and Kehr, 1976) hemitranssection reduced the formation of 5-HTP in the lesioned forebrain by 34%. In the present investigation, however, 5-HTP accumulation was also reduced in the intact forebrain by 29% as compared to sham operated controls. We have no explanation for this unexpected finding at present. As compared to hemisection controls neither LSD in the two doses tested nor LSD in combination with haloperidol led to any noticeable changes in 5-HTP formation on the lesioned side, however, in the intact forebrain LSD at the dose of 0.5 mg/kg decreased the hydroxylation of tryptophan when given alone ($P < 0.01$) or in combination with haloperidol ($P < 0.05$, Fig. 3b).

Effect of Apomorphine, LSD and Lisuride after Pretreatment with Reserpine

In a second model we have used reserpine in order to depress monoaminergic neurotransmission. Rats were treated with reserpine, 5 mg/kg i.p., 24 h prior to LSD or lisuride which were injected in doses of 1, 10 and 100 µg/kg i.p., 35 min before death. All

Table 1. Effect of lisuride and LSD on dopa accumulation in rat neocortex after pretreatment with reserpine. Reserpine, 5 mg/kg was administered i.p. 24 h, NSD 1015, 100 mg/kg i.p. 30 min before death and the test compound 5 min prior to NSD 1015

	Dopa, ng/g	n	P
A. Control	72 ± 3	8	
B. Reserpine	155 ± 8	8	vs. A < 0.01
C. Reserpine + Lisuride, 1 µg/kg i.p.	161 ± 9	4	vs. B not significant
D. Reserpine + Lisuride, 10 µg/kg i.p.	149 ± 4	4	vs. B not significant
E. Reserpine + Lisuride, 100 µg/kg i.p.	159 ± 2	4	vs. B not significant
F. Reserpine + LSD, 1 µg/kg i.p.	151 ± 3	4	vs. B not significant
G. Reserpine + LSD, 10 µg/kg i.p.	158 ± 3	4	vs. B not significant
H. Reserpine + LSD, 100 µg/kg i.p.	160 ± 4	4	vs. B not significant

Shown are the means ± S.E.M.
Statistics: analysis of variance, Scheffé-test

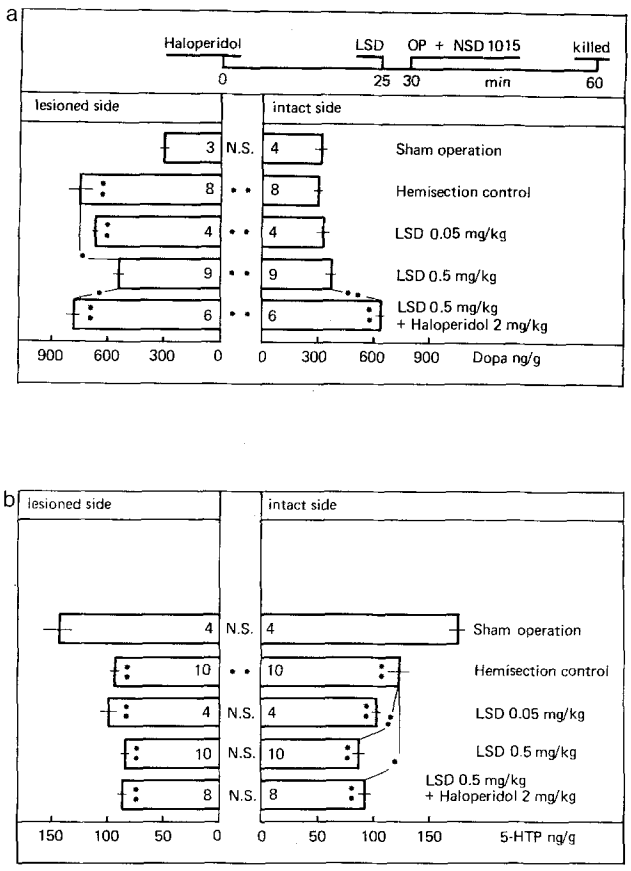


Fig. 3. Effect of LSD alone or in combination with haloperidol on the accumulation of dopa (a) and 5-hydroxytryptophan (b) in rat forebrain after cerebral hemitranssection and treatment with NSD 1015, 100 mg/kg i.p. Shown are the means ± S.E.M. The number of experiments is indicated in the columns. Statistics: For comparison of lesioned vs. intact side the paired *t*-test was used. Separate analysis of variance followed by Scheffé-test was used for comparison of treatments on lesioned and on intact side $^{*}P < 0.05$, $^{**}P < 0.01$

animals received NSD 1015 (100 mg/kg i.p.) 30 min before decapitation.

Reserpine stimulated dopa formation as compared to NSD 1015 controls in the corpus striatum, the limbic system as well as the neocortex. In the corpus striatum the lowest dose of lisuride was inactive while the larger doses (10 and 100 µg/kg) of lisuride significantly reduced the reserpine-induced increase in dopa formation by 27% and 56%, respectively (Fig. 4a). LSD at 1 and 10 µg/kg did not antagonize the reserpine-induced increase in dopa formation, however, 100 µg/kg led to a 29% reduction in tyrosine hydroxylation.

In the dopamine-rich part of the limbic system lisuride at doses of 10 and 100 µg/kg antagonized the reserpine-induced stimulation of dopa formation by 28% and 22%, respectively; it was inactive at a dose of 1 µg/kg.

In this experiment, none of the doses of LSD led to any significant changes in tyrosine hydroxylation in the limbic forebrain (Fig. 4b). In the rat neocortex neither lisuride nor LSD altered the reserpine-induced stimulation of tyrosine hydroxylation (Table 1).

Changes in tyrosine levels were slight and statistically not significant, except a marginal increase in tyrosine after LSD (10 µg/kg) in the limbic system and the neocortex (data not shown).

In a further series of experiments using reserpinized rats we investigated the interaction of both ergot derivatives with the dopamine receptor-stimulating agent apomorphine.

Table 2 shows that apomorphine and lisuride were equipotent in antagonizing the effect of reserpine on dopa formation in corpus striatum and the limbic system while LSD was much weaker.

Table 2. Dopa accumulation after pretreatment with reserpine: Interaction of lisuride or LSD with apomorphine. Reserpine, 5 mg/kg was administered i.p. 24 h, NSD 1015, 100 mg/kg i.p. 30 min before death and apomorphine, LSD or lisuride 5 and 4 min, respectively, prior to NSD 1015

	Dopa ng/g striatum	*P*	Dopa ng/g limbic system	
A. Saline control (6)	1.424 ± 55		717 ± 16	
B. Apomorphine 0.1 mg/kg i.p. (5)	454 ± 26	vs. A < 0.01	364 ± 23	vs. A < 0.01
C. LSD 0.1 mg/kg i.p. (6)	797 ± 28	vs. A < 0.01	537 ± 15	vs. A < 0.01
D. Lisuride 0.1 mg/kg i.p. (6)	466 ± 16	vs. A < 0.01	390 ± 18	vs. A < 0.01
E. Apomorphine + LSD (6)	549 ± 27	vs. A < 0.01 vs. B < 0.1 vs. C < 0.01	493 ± 24	vs. A < 0.01 vs. B < 0.05 vs. C < 0.1
F. Apomorphine + Lisuride (6)	457 ± 16	vs. A < 0.01 vs. B > 0.1 vs. D > 0.1	344 ± 40	vs. A < 0.01 vs. B > 0.1 vs. D > 0.1

Shown are the means ± S.E.M., figures in brackets indicate number of experimental groups. Statistics: analysis of variance, Scheffé-test

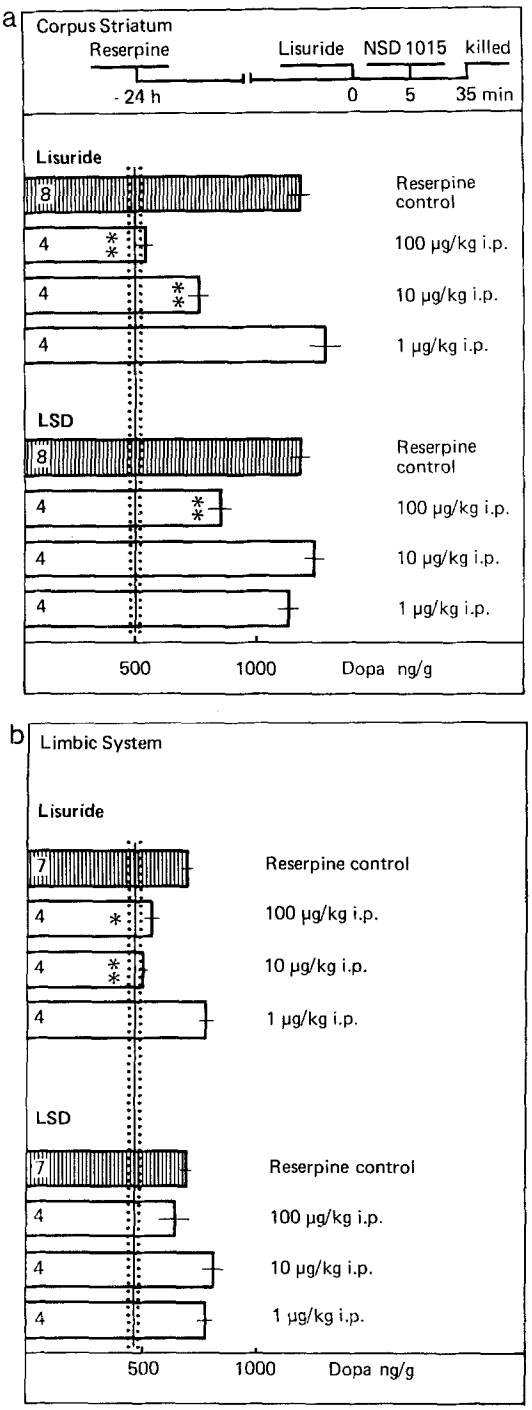


Fig. 4. Effect of lisuride and LSD on dopa formation in c. striatum (b) and the dopamine-rich part of the limbic system (a) of rat brain 24 h after pretreatment with reserpine. All animals were given an i.p. injection of NSD 1015, 100 mg/kg i.p., 30 min before death as indicated. Reserpine was injected at a dose of 5 mg/kg i.p., lisuride and LSD were given i.p. 7 min prior to NSD 1015, and the brain parts were analyzed for dopa. Each experiment comprises pooled brain parts of two rats. Shown are the means ± S.E.M. The number of experiments is indicated in the columns. The vertical line and the stippled lines indicate the mean ± S.E.M. of the NSD 1015 control (no reserpine). Statistics: analysis of variance followed by the Scheffé-test. Stars indicate significant differences vs. reserpine control * $P < 0.05$, ** $P < 0.01$

When lisuride was given in addition to apomorphine, dopa accumulation was identical to that induced by either drug alone. However, when LSD was applied in combination with apomorphine the effect of apomorphine appeared to be counteracted by LSD.

The concomitant determination of tyrosine concentrations showed only slight changes which did not reach statistical significance (data not shown).

DISCUSSION

The present data in agreement with those of Persson (1977) demonstrate that LSD increases tyrosine hydroxylation in the brain of intact animals. In view of the dopamine receptor agonistic action of LSD which has been proposed on the basis of behavioral experiments (Pieri et al., 1974) and neurochemical experiments (von Hungen et al., 1975; Kelly and Iversen, 1975; Da Prada et al., 1975) the accelerating effect of LSD on dopa formarion does not fit into the concept of receptor-mediated negative feedback control of catecholamine synthesis, since a dopamine receptor stimulating agent should inhibit dopamine synthesis. In this respect LSD clearly differed from the well-known dopamine receptor stimulating agent apomorphine (Carlsson et al., 1977) and the ergot derivative lisuride (Kehr, 1977a) which both inhibit dopamine synthesis. It is unlikely that the small increase in brain tyrosine concentration (Fig. 2a) found in the present study after high doses of LSD and which was not observed in earlier experiments with apomorphine and lisuride contributed to the enhanced dopa formation following LSD since tyrosine hydroxylase is saturated with the substrate tyrosine under normal conditions (Carlsson et al., 1972).

After interruption of impulse flow in dopamine neurons by axotomy, however, LSD at a dose of 0.5 mg/kg did not enhance but antagonized the increase in tyrosine hydroxylation known to occur due to decreased activation of presynaptic receptors (Kehr et al., 1977). Since the effect of LSD was fully reversed by the dopamine receptor blocking agent haloperidol, we assume that LSD was acting by stimulating dopamine receptors. In these experiments the action of LSD was qualitatively comparable to apomorphine (Kehr et al., 1977) and lisuride (Kehr, 1977a).

Depression of monoaminergic neurotransmission by treatment with reserpine increases catecholamine synthesis in rat brain areas by two different mechanisms. De novo synthesis of enzyme molecules is responsible for the late increase in tyrosine hydroxylase activity, slow in onset and lasting for several days (Mueller et al., 1969; Thoenen et al.,

1969) while the initial and pronounced increase is suggested to be solely due to receptor mediated feedback involving an activation of existing enzyme molecules (Carlsson and Lindqvist, 1977).

In rats pretreated with reserpine, LSD reduced the increase in dopa accumulation in the dopamine-rich areas c. striatum and limbic system (Fig. 3, Table 2). Doses more than 10 times higher than for the structural congener lisuride were necessary to produce the same degree of inhibition of dopa formation after reserpine. The present finding of a strong inhibitory action of lisuride on reserpine-induced dopa formation is in agreement with recent data of Loos, Halbhübner and Herken (personal communication) showing that lisuride was very efficacious in counteracting the reserpine-induced muscle rigidity. The later results also support the view that lisuride possesses strong and LSD weak dopamine receptor stimulating properties.

When the reserpine-induced stimulation of tyrosine hydroxylation was suppressed by apomorphine (Table 2) LSD but not lisuride antagonized the action of apomorphine in c. striatum and the limbic system indicating dopamine receptor blocking properties of LSD as also shown in a recent publication by Persson (1977).

Thus, LSD appears to be an agonist as well as an antagonist of dopamine receptors depending on the actual receptor activity. Apart from the present experiments agonistic properties of LSD have been shown in other investigations only when the occupancy of the dopamine receptors was low either after destruction of the dopamine neurons with 6-hydroxydopamine (Pieri et al., 1974; Kelly and Iversen, 1975), depletion of dopamine stores by reserpine (Grabowska et al., 1974; Persson, 1977) or inhibition of impulse flow by γ-butyrolactone (Persson, 1977). On the other hand, antagonistic properties were demonstrated under normal and increased occupancy of the dopamine receptor, e.g. after pretreatment with apomorphine (Persson, 1977).

Binding studies on dopamine receptors in vitro lend further support for the partial agonistic property of LSD (Creese et al., 1976).

Earlier data from this laboratory indicated that low doses of LSD as well as lisuride reduced the impulse-induced release of dopamine in vivo while higher doses caused an increased release of dopamine which was interpreted as being due to preferential stimulation of dopamine receptors at low doses and blockade of dopamine receptors at high doses (Kehr, 1977a).

By comparison with LSD the present data indicate that lisuride has very weak – if any – dopamine receptor blocking properties since the inhibitory effect of apomorphine on dopa accumulation was neither enhanced nor augmented (Table 2).

At the doses tested the effect of LSD and lisuride appeared to be restricted to the dopamine neurons since dopa accumulation was not affected in the noradrenaline-rich neocortex (Table 1).

The inhibitory effect of high doses of LSD on tryptophan hydroxylase in vivo in mice has been shown earlier (Carlsson and Lindqvist, 1972) and could be shown here in the rat also for doses as low as 50 µg/kg i.p. The increase in tryptophan concentration which has been described earlier by Tonge and Leonard (1970) and Freedman and Boggan (1974) is not understood at present. Possibly, tryptophan is increased in order to compensate for decreased 5-HTP formation. The simultaneous elevation of tyrosine concentration – confirming earlier data by Smith et al. (1975) – offers the alternative explanation that LSD increases the availability of aromatic amino acids in the CNS by a common mechanism.

Hemitransection abolished the inhibitory effect of LSD on tryptophan hydroxylation. Haloperidol changed the effect of LSD neither on the lesioned nor on the intact side. Thus, it appears unlikely that the effect of LSD on tryptophan hydroxylation was indirectly or mediated by a dopamine-dependent mechanism.

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