European Journal of Pharmacology, 93 (1983) 213–220
Elsevier

AD

INFLUENCE OF PSYCHOTOMIMETICS AND LISURIDE ON SYNAPTOSOMAL DOPAMINE RELEASE IN THE NUCLEUS ACCUMBENS OF RATS

LÁSZLÓ HETEY *, RAINER SCHWITZKOWSKY and WOLFGANG OELSSNER

Institute of Pharmacology and Toxicology of Charité, Humboldt University, Berlin, G.D.R.

Received 7 June 1983, accepted 12 July 1983

L. HETEY, R. SCHWITZKOWSKY and W. OELSSNER, *Influence of psychotomimetics and lisuride on synaptosomal dopamine release in the nucleus accumbens of rats*, European J. Pharmacol. 93 (1983) 213–220.

In superfusion experiments with a crude synaptosomal fraction from the nucleus accumbens of rats, lysergic acid diethylamide, mescaline and N,N-dimethyltryptamine (representing different chemical classes of psychotomimetics) produced a concentration-related inhibition of K^+-evoked [^{3}H]dopamine release whereas spontaneous release remained unchanged. The nonpsychotomimetic ergoline lisuride tested at the same concentration range did not modulate spontaneous or K^+-evoked [^{3}H]dopamine release. The inhibitory effects of the psychotomimetics tested were antagonized by equal concentrations of haloperidol or methiothepine. It is postulated that the effects of psychotomimetics on DA release were triggered via simultaneous action at presynaptic dopamine and 5-hydroxytryptamine receptors which are located at dopamine nerve endings in the nucleus accumbens.

Dopamine release Nucleus accumbens Psychotomimetics Lisuride Haloperidol Methiothepine

1. Introduction

Dopamine (DA) receptor-mediated inhibition of the stimulated release of previously accumulated [^{3}H]DA has been demonstrated in superfusion experiments with striatal slices and synaptosomes of rats (for review and discussion of conflicting data see Starke, 1978) and with synaptosomes from the nucleus accumbens of rats (Hetey et al., 1982).

Recently Ennis et al. (1981) reported an inhibition of DA release in the rat striatum by a series of indoleamines and a concentration-dependent attenuation of these inhibitory effects by 5-hydroxytryptamine (5HT) antagonists. A similar phenomenon has been shown in our experiments with synaptosomes from the nucleus accumbens of rats (Hetey et al., 1982). Both results suggest the presence of inhibitory 5HT receptors at DA nerve endings at least in the striatum and nucleus accumbens of rats.

Psychotomimetics were shown to have approximately similar affinities to 5HT and DA receptors in the brain but data regarding their actions upon the DA system are scarce (for review see Freedman and Boggan, 1982). Push-pull experiments with cats showed that lysergic acid diethylamide (LSD) depressed the DA outflow (Da Prada et al., 1975), decreased the concentration of homovanillic acid (HVA) in whole brain (Pieri et al., 1978) and inhibited the K^+-stimulated DA release from superfused synaptosomes from nucleus accumbens of LSD-pretreated rats (Hetey and Quiring, 1980). On the other hand biochemical evidence suggests indirectly that the synthetic psychotomimetics N,N-dimethyltryptamine (DMT) could stimulate DA release (Waldmeier and Maître, 1977). However, the results from such in vivo experiments are difficult to interpret and no clearcut conclusions can be drawn about either the site of action, or the presumed involvement of

* To whom all correspondence should be addressed: Institute of Pharmacology and Toxicology of Charité, Humboldt University, DDR 1040 Berlin, Pf. 140, Clara-Zetkin-Str. 94, German Democratic Republic.

5HT and Da receptors (Freedman and Boggan, 1982).

The occurrence of DA autoreceptors as well as of 5HT heteroreceptors at DA nerve endings in the nucleus accumbens provides the opportunity to elucidate the actions of psychotomimetics upon Da release and to characterize the type of receptor involved. We investigated the effects of three psychotomimetics from different chemical classes, the ergoline compound LSD, the phenethylamine derivate mescaline and the indoleamine DMT in comparison to lisuride, a nonpsychotomimetic ergoline structurally related to LSD with potent 5HT and DA agonist effects (Freedman and Boggan, 1982). For the characterization of the receptors involved we used the DA antagonist haloperidol and the 5HT antagonist methiothepine, the most active and specific compound in antagonizing the inhibitory 5HT effects on DA release from synaptosomes of the nucleus accumbens (Hetey et al., 1982) and on 5HT release in various brain areas (Cerrito and Raiteri, 1979; Göthert, 1980; Hetey et al., 1982).

Finally we carried out some comparative release experiments without inhibition of monoamine oxidase (MAO). The MAO inhibitors were shown to change the distribution of DA into the different compartments of presynaptic terminals and could therefore induce artifactual results (Arbilla and Langer, 1980).

2. Materials and methods

2.1. Tissue preparation

Male Wistar rats (VEB Versuchstierproduktion Schönwalde) housed under standard conditions (temperature $22 \pm 2°C$, 12 h light/dark schedule, food and water ad libitum) were sacrificed by immersion into liquid nitrogen for about 7 s, the brains rapidly removed and the nuclei accumbens dissected out on ice-cooled Petri dishes. For preparation of a crude synaptosomal fraction the tissue was homogenized (teflon pestle, clearance 0.03 mm, 10 strokes) in 0.32 M sucrose containing (mM) Na_2HPO_4 2.0; KH_2PO_4 0.7; $MgCl_2$ 1.0; disodium EDTA 3.0; pH 7.3. Nuclei and cell debris were removed by centrifugation ($1000 \times g$ for 8 min; 2-4°C).

2.2. Synaptosomal [^{3}H]dopamine release

The synaptosomal suspension was transferred to a modified McIlwain uptake buffer saturated with 5% carbon dioxide in oxygen, containing (mM) KCl 1.7; KH_2PO_4 1.3; Na_2HPO_4 10.4; NaCl 130.0; $MgSO_4$ 1.3; $CaCl_2$ 1.3; pargyline 0.125; disodium EDTA 0.2; ascorbic acid 1.1; sucrose 17.3; glucose 11.0 (McIlwain, 1951), and adjusted to pH 7.3. The synaptosomal suspension was incubated with [^{3}H]DA (10^{-7} M) for 8 min at 37°C, divided into two equal parts, placed on GFB Whatman filters and transferred into two superfusion chambers (inner volume 0.4 ml) as described recently (Hetey and Quiring, 1980). The synaptosomes were superfused at 37°C at a rate of 0.5 $ml \cdot min^{-1}$ at first for 10 min with a McIlwain normal buffer with a doubled concentration of Ca^{2+} followed for 8 min by superfusion with normal buffer to which the drugs to be tested were added immediately before starting the superfusion. Synaptosomes were depolarized for 4 min in a McIlwain buffer containing 30 mM K^+ with isomolar replacement of Na^+. An additional 10 min superfusion with normal buffer containing the drugs finished the release experiment.

Superfusate fractions were collected every 2 min and their radioactivity as well as the residual radioactivity in the synaptosomes at the end of the experiments was determined by liquid scintillation counting (LKB, model 1210, ultrobeta). For calculation of [^{3}H]DA release, the difference between the K^+-stimulated and the virtually unstimulated release was determined in relation to the total amount of radioactivity present in the synaptosomes at the onset of the stimulation period.

In the experiments without MAO inhibition the same conditions were used with the exception that the uptake and superfusion buffer did not contain pargyline and that 3 effluent fractions were collected each into 0.6 ml of 0.6 n acetic acid containing 0.6% ascorbic acid: the spontaneous release fraction before and after the stimulation period and the K^+-stimulated release fraction (each for 6 min beginning at 12, 18 and 24 min of

superfusion). After superfusion, the synaptosomes were extracted with 0.1 n acetic acid containing 0.1% ascorbic acid and both the effluent fractions and the extracts were but, at pH 4, on Dowex 50 WX8-H^+ ion-exchange columns for DA separation (Taylor and Laverty, 1969). Column recovery for DA was 86%. For calculating the K^+-evoked release of [^{3}H]DA the average DA radioactivity of the spontaneous release fractions was subtracted from the corresponding DA value of the K^+-stimulated fraction and expressed as the percentage of the [^{3}H]DA activity in the synaptosomes at the onset of K^+ stimulation.

Statistical analysis was performed according to Wilcoxon, Mann and Whitney (based on Wilcoxon, 1947).

2.3. Materials

The following drugs were used: [ethyl-1-^{3}H(N)]-dopamine (spec. activity 21.8 Ci/mmol; New England Nuclear, Boston); N,N-dimethyltryptamine (Sigma, St. Louis); haloperidol (G. Richter, Budapest); lysergic acid diethylamide tartrate (SPOFA, Prague); lisuride hydrogen maleate (gift from Schering AG, West-Berlin), mescaline sulfate (Merck, Darmstadt); methiothepine maleate (gift from Hoffmann-La Roche, Basel); pargyline hydrochloride (VEB Fahlberg-List, Magdeburg).

Haloperidol and DMT were dissolved in a few drops of 2 N acetic acid and the pH was corrected after adding the buffer to the final volume. The other drugs were dissolved in distilled water and stock solutions stored for a maximum of 1 week at −18°C. Lisuride was dissolved immediately before use.

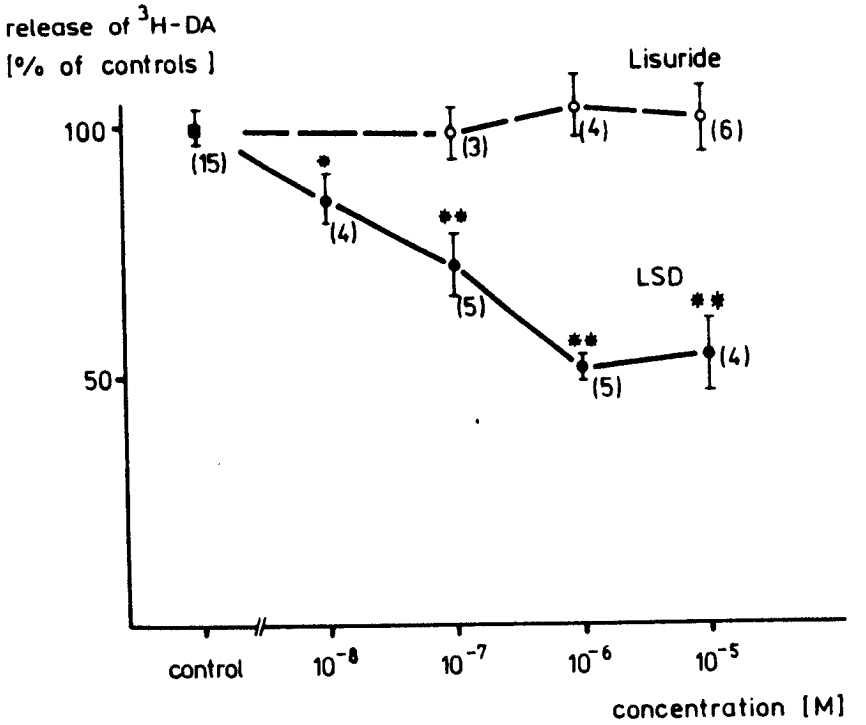

Fig. 1. Concentration-related inhibition by LSD and lack of inhibitory effects of lisuride on 30 mM K^+-evoked [^{3}H]DA release from superfused synaptosomes of the nucleus accumbens; results expressed as percent of controls; 100% = 15.30% of total radioactivity. The values represent mean ± S.E.M.; number of experiments in parentheses. * $P < 0.05$; ** $P < 0.01$ vs. controls, according to Wilcoxon, Mann and Whitney.

3. Results

3.1. Influence of LSD and lisuride on DA release

Superfusing synaptosomes from the nucleus accumbens, preloaded with [^{3}H]DA, with a solution containing 30 mM K^+ produced a marked increase in tritium overflow which was shown to be mainly Ca^{2+}-dependent (Hetey and Quiring, 1980). LSD added 10 min after the onset of the superfusion with normal buffer did not change the spontaneous release. The K^+-evoked tritium release, however, was inhibited by LSD in a concentration-related manner (fig. 1). There was already a significant reduction with a concentration of 10^{-8} M LSD. The maximum inhibition to 51.5% of the controls was caused by a concentration of 10^{-6} M LSD and an IC_{50} value representing half-maximum inhibition of about 7×10^{-8} M LSD was calculated. On the other hand, lisuride over the concentration range 10^{-7} to 10^{-5} M did not induce any significant change in the spontaneous as well as in the K^+-evoked tritium release (fig. 1).

3.2. Influence of mescaline and DMT on DA release

Mescaline and DMT did not change the spontaneous release over the concentration range $5 \times$

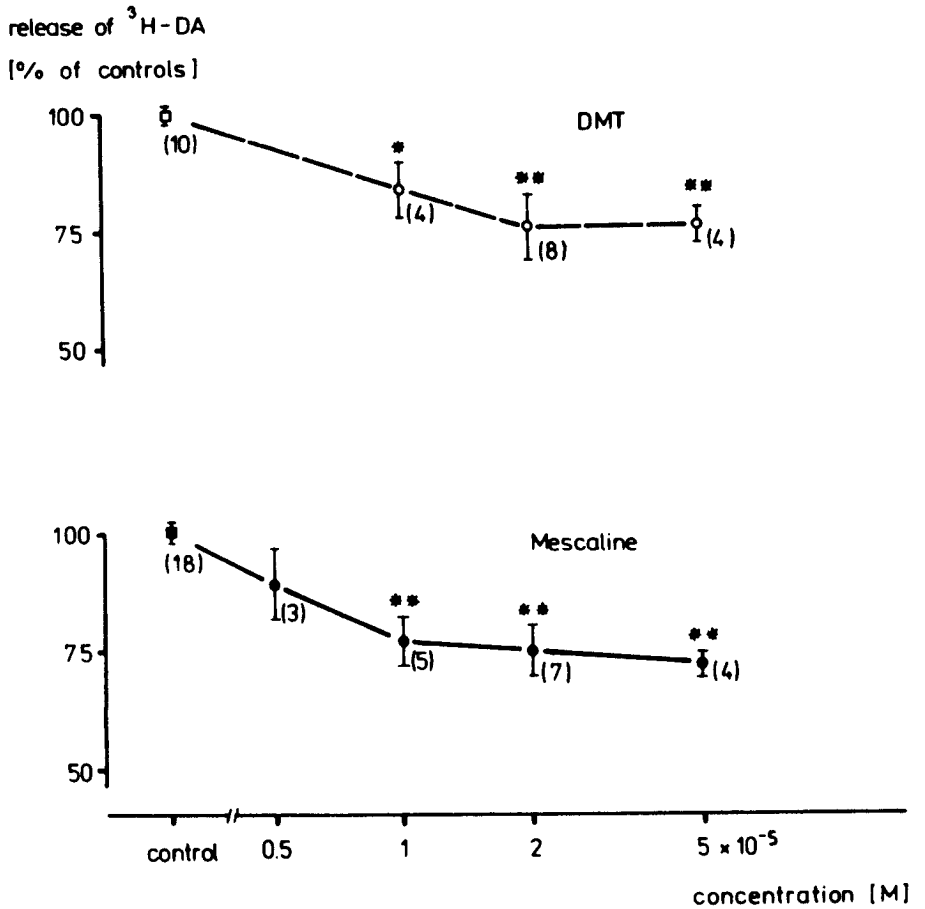

Fig. 2. Concentration-related inhibition by DMT and mescaline of 30 mM K^+-evoked [^{3}H]DA release from superfused synaptosomes of the nucleus accumbens, expressed as percent of controls; 100% = 14.45% and 15.35% of total radioactivity. The values represent mean ± S.E.M.; number of experiments in parentheses. * $P < 0.05$; ** $P < 0.01$ vs. controls, according to Wilcoxon, Mann and Whitney.

10^{-6} to 5×10^{-5} M. Both psychotomimetics however produced a concentration-dependent inhibition of the K^+-evoked tritium release with similar profiles (fig. 2). A rather high concentration, i.e. 10^{-5} M, was needed to cause a significant decrease. The maximum inhibitory effects did not exceed 28% with mescaline (IC_{50} value of about 6×10^{-6} M) and 24% with DMT (IC_{50} value of about 7×10^{-6} M). With bith compound a plateau seemed to be reached at a concentration of 2×10^{-5} M.

3.3. Actions of haloperidol and methiothepine upon psychotomimetic-induced inhibition of DA release

At the concentrations used, neither haloperidol nor methiothepine produced significant changes in the spontaneous overflow and K^+-evoked tritium release was only slightly and non-significantly increased. However, simultaneous superfusion with haloperidol and with each of the psychotomimetics caused a pronounced increase in the spontaneous tritium release. These effects could be prevented by adding cocaine (4×10^{-5} M) which was therefore used throughout these experiments with haloperidol. Additional experiments excluded the

TABLE 1

Attenuation by haloperidol and methiothepine of the inhibitory effects of LSD, mescaline and DMT on 30 mM K^+-stimulated [^{3}H]DA release from superfused synaptosomes of the nucleus accumbens of rats. Values represent means ± S.E.M.; (n) = number of experiments. For further details see Methods. [a] $P < 0.05$; [b/c] $P < 0.01$ vs. controls and psychotomimetics, respectively, according to Wilcoxon, Mann and Whitney.

Drugs	Final concentration (μM)	Surplus of K^+-stimulated tritium release, % of total radioactivity, (n)	% of controls
Controls		15.30 ± 0.89 (15)	100
LSD	2	9.36 ± 0.54 (16) [b]	61
LSD	2	13.80 ± 0.64 (5) [c]	90
+ haloperidol	1		
LSD	2	12.10 ± 0.70 (5) [a]	79
+ haloperidol	0.5		
LSD	2	14.73 ± 1.41 (5) [c]	96
+ methiothepine	1		
LSD	2	13.50 ± 1.77 (5) [a]	88
+ methiothepine	0.5		
Haloperidol	1	15.67 ± 1.47 (4)	102
Methiothepine	1	16.19 ± 1.12 (3)	106
Controls		14.82 ± 0.53 (5)	100
Mescaline	20	10.65 ± 0.63 (5) [b]	72
Mescaline	20	15.47 ± 0.72 (4) [c]	104
+ halopetidol	5		
Mescaline	10	18.13 ± 0.78 (4) [c]	122
+ methiothepine	5		
DMT	20	9.92 ± 1.29 (4) [b]	67
DMT	20	13.08 ± 0.50 (5) [a]	88
+ haloperidol	5		
DMT	20	17.20 ± 0.40 (3) [c]	116
+ methiothepine	5	17.20 ± 0.40 (3) [c]	116
Haloperidol	5	15.92 ± 0.88 (4)	107
Methiothepine	5	16.86 ± 1.14 (4)	114

possibility that cocaine changed the tritium overflow and the inhibition of K^+-evoked release produced by the psychotomimetics (results not shown).

Haloperidol as well as methiothepine antagonized concentration-dependently the inhibitory effects of LSD 2×10^{-6} M (table 1). In both cases half-equimolar concentrations of the antagonists were sufficient to block the LSD effect completely. The inhibition of K^+-evoked tritium release induced by mescaline and DMT 2×10^{-5} M was antagonized by haloperidol and methiothepine 5×10^{-6} M, respectively, in a quite similar manner (table 1).

3.4. Influence of LSD on K^+-stimulated DA release without MAO inhibition

In the experiments without pargyline the content of [^{3}H]DA in the spontaneous release fractions was not different before and after the stimulation period and averaged 49.2 ± 4.6% of the total ^{3}H-content in the effluents (n = 10, mean ± S.E.M.). The K^+-stimulated release fraction contained, in excess of the spontaneously released DA, 93.2 ± 3.2% [^{3}H]DA (n = 5). Similarly, most of the synaptosomal radioactivity at the end of the superfusion was DA (88.4 ± 5.7%, n = 5). The K^+-stimulated DA release was 12.1 ± 1.4% of the synaptosomal DA content. De Langen and coworkers (1979) had obtained similar results in comparable experiments with synaptosomes of rat striatum. Like the K^+-stimulated Da release, the influence of LSD and the antagonists on release was in the same range as in the experiments with pargyline (see table 2).

4. Discussion

LSD, mescaline and DMT, representing different chemical types of psychotomimetics, produced a qualitatively similar concentration-dependent inhibition of K^+-stimulated tritium release from superfused synaptosomes preloaded with [^{3}H]DA. Since the basal tritium overflow remained unchanged in the presence of the psychotomimetics tested and the uptake inhibitor cocaine did not modulate the inhibitory effects of the psychotomimetics which, however, were blocked by a DA and a 5HT antagonist, respectively, it seems most likely that the changes in the evoked overflow of tritium reflect a receptor-mediated modulation of transmitter release (for review see Starke, 1978). The pronounced differences in potency of the psychotomimetics tested correspond to similar differences seen in electrophysiological, biochemical and binding studies, in behavioural experiments and with respect to the hallucinogenic potency in man (for reviews see Aghajanian, 1982; Freedman and Boggan, 1982). Our results are in accordance with findings of Ennis et al. (1981) that the psychotomimetic 5-methoxy-N,N-dimethyltryptamine

TABLE 2

Antagonism by haloperidol and methiothepine of the inhibition by LSD of 30 mM K^+-stimulated [^{3}H]DA release from superfused synaptosomes without MAO inhibition. Values represent means ± S.E.M.; [b/c] $P < 0.01$ vs. controls and LSD, respectively, according to Wilcoxon, Mann and Whitney. For further details see Methods.

Drugs	Final concentration (μM)	Surplus of K^+-stimulated [^{3}H]DA release, % of total [^{3}H]DA (n)	% of controls
Controls		12.10 ± 1.40 (5)	100
LSD	2	6.78 ± 1.65 (5) [b]	56
LSD	2	11.49 ± 0.82 (5) [c]	95
+ haloperidol	1		
LSD	2	10.16 ± 1.30 (5) [c]	84
+ methiothepine	1		
Haloperidol	1	13.43 ± 2.45 (4)	111
Methiothepine	1	11.86 ± 0.73 (4)	98

inhibits K^+-evoked DA release from striatal slices. Moreover, our results appear to confirm reports of a reduced DA overflow seen in push-pull experiments (Da Prada et al., 1975) and a decrease in HVA (Pieri et al., 1978) and in the formation of 3-methoxytyramine (Kehr, 1977) after systemic administration of LSD. However, there are also conflicting data (Keller et al., 1978) and the dosage level seems to be rather important. A significant decrease in the K^+-stimulated DA release from superfused synaptosomes prepared from the nucleus accumbens of LSD-pretreated rats could be demonstrated only after i.p. injections of 0.5 mg/kg LSD, whereas 0.1 mg/kg remained ineffective (Hetey and Quiring, 1980). Under special conditions, i.e. after pretreatment with reserpine or cerebral hemisection, LSD may already act at lower doses upon presynaptic receptors at DA nerve endings as has been shown by the finding of an inhibition of the increased dopa accumulation (Persson, 1977; Kehr and Speckenbach, 1978). Although LSD and the other two psychotomimetics were shown to inhibit DA release in vitro, some of their effects on the DA system in vivo may be triggered indirectly. Thus, 50 ng LSD microinjected into the medial raphe nucleus of conscious rats increased the stimulated DA release in the nucleus accumbens significantly, obviously by attenuating an inhibitory 5HT input to DA neurons in the ventral tegmental area (Oelssner et al., 1982).

Decreased levels of striatal HVA and a more pronounced decrease of dihydroxyphenylacetic acid after DMT have been interpreted as a superimposition of MAO inhibitory properties and a DA releasing action of DMT (Waldmeier and Maître, 1977). However, close inspection on the experimental data does not provide direct evidence for an increased DA release and according to our in vitro results inhibitory rather than stimulatory actions of DMT upon DA release must be taken into account. On the other hand the lack of inhibitory effects of lisuride suggests that the marked decrease in HVA at both low and high doses (Keller et al., 1978) and the delayed disappearence of DA after α-methyl-p-tyrosine (Kehr, 1977) depend on the stimulation of postsynaptic DA receptors and triggering of receptor-coupled feedback mechanisms. Furthermore, Kebabian and Kebabian (1978) reported that lisuride did not inhibit striatal tyrosine hydroxylase in vitro which appears to provide further evidence for the lack of presynaptic DA effects of lisuride.

The inhibition of DA release by LSD was antagonized by the DA antagonist haloperidol as well as by the 5HT antagonist methiothepine in a concentration-dependent and highly specific manner. A qualitatively similar antagonism could be demonstrated toward the inhibitory effects of mescaline and DMT. The specifity of the DA antagonistic properties of haloperidol is generally accepted. In contrast to other much less potent or even inactive 5HT antagonists, methiothepine was extremely potent in attenuating the inhibitory effects of 5HT on DA release (Hetey et al., 1982) and on its own release in superfusion experiments with synaptosomes from the hypothalamus (Cerrito and Raiteri, 1979) and the nucleus accumbens (Hetey et al., 1982), and with brain cortex slices (Göthert, 1980).

The corresponding inhibitory effects of three psychotomimetics of different chemical types, the lack of effect of lisuride and the equal potency of a DA and a 5HT antagonist represent a rather unusual combination of effects. The possibility that at least two distinct receptor types occur is supported by the finding that, in each case, inhibitory effects of the transmitters DA and 5HT on synaptosomal DA release as well as on synaptosomal tyrosine hydroxylase activity in the nucleus accumbens can be blocked only by the specific antagonist haloperidol and methiothepine, respectively (Hetey et al., 1982; Hetey, Kudrin, Shemanow, Rayevsky and Oelssner, submitted for publication). The psychotomimetics may interact simultaneously with both receptor types, however, it is only poorly understood why the blockade of one receptor by the specific antagonist should also counteract effects mediated by the other receptor. Moreover, the failure of lisuride to exert inhibitory actions despite its more pronounced postsynaptic DA and 5HT agonist properties points to an effect specific to psychotomimetics. It seems that agents capable of stimulating both DA and 5HT receptors simultaneously can contribute to the triggering of hallucinogen-specific activities as shown with an in vitro moel. The antagonism of the hallucinogen-in-

duced effects by each specific blocker may be explained by assuming that the hallucinogenic molecule will be sterically hindered from acting via the other unoccupied receptor. Another possibility is that the two presynaptic receptors interact allosterically and therefore recognition of the hallucinogen is not possible at the unoccupied receptor part. More detailed experiments are needed to get a better insight into the postulated specific actions of psychotomimetics at the biochemical level.

Acknowledgement

The authors thank Mrs. Heidrun Engel for excellent technical assistance.

References

Aghajanian, G.K., 1982, Neurophysiologic properties of psychotomimetics, in: Psychotropic Agents, Part III, eds. F. Hoffmeister and G. Stille (Springer, Berlin-Heidelberg-New York) p. 89.

Arbilla, S. and S.Z. Langer, 1980, Influence of monoamine oxidase inhibition on the release of ^{3}H-dopamine elicited by potassium and by amphetamine from the rat substantia nigra and corpus striatum, Naunyn-Schmiedeb. Arch. Pharmacol. 311, 45.

Cerrito, F. and M. Raiteri, 1979, Serotonin release is modulated by presynaptic autoreceptors, European J. Pharmacol. 57, 427.

Da Prada, N., A. Saner, W.P. Burkard, G. Bartholini and A. Pletscher, 1975, Lysergic acid diethylamide; evidence for stimulation of cerebral dopamine receptors, Brain Res. 94, 67.

De Langen, C.D.J., J.C. Stoof and A.H. Mulder, 1979, Studies on the nature of the releasable pool of dopamine in synaptosomes from rat corpus striatum: depolarization-induced release of ^{3}H-dopamine from superfused synaptosomes labelled under various conditions, Naunyn-Schmiedeb. Arch. Pharmacol. 308, 41.

Ennis, C., J.D. Kemp and B. Cox, 1981, Characterization of inhibitory 5-hydroxytryptamine receptors that modulate dopamine release in the striatum, J. Neurochem. 36, 1515.

Freedman, D.X. and W.O. Boggan, 1982, Biochemical pharmacology of psychotomimetics, in: Psychotropic Agents, Part III, eds. F. Hoffmeister and G. Stille (Springer, Berlin-Heidelberg-New York) p. 57).

Göthert, M., 1980, Serotonin-receptor-mediated modulation of Ca^{2+}-dependent 5-hydroxytryptamine release from neurones of the rat brain cortex, Naunyn-Schmiedeb. Arch. Pharmacol. 314, 223.

Hetey, L., K. Drescher and W. Oelssner, 1982, Different influence of antipsychotics and serotonin (5HT) antagonists on presynaptic receptors modulating the synaptosomal release of dopamine and 5HT, Wiss. Zeitschr. Humboldt-Univ., 31, 487.

Hetey, L. and K. Quiring, 1980, Synaptosomal uptake and release of dopamine and 5-hydroxytryptamine in the nucleus accumbens in vitro following in vivo administration of LSD in rats, Acta Biol. Med. Germ. 39, 889.

Kebabian, J.W. and P.R. Kebabian, 1978, Lergotrile and lisuride: In vivo dopaminergic agonists which do not stimulate the presynaptic dopamine autoreceptor, Life Sci. 23, 2199.

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

Keller, H.H., W.P. Burkard, L. Pieri, E.P. Bonetti and M. Da Prada, 1978, Lisuride- and LSD-induced changes of monoamine turnover in the rat brain, Adv. Biochem. Psychopharmacol. 19, 393.

McIlwain, H., 1951, Metabolic response in vitro to electrical stimulation of sections of mammalian brain, Biochem. J. 49, 382.

Oelssner, W., H. Fink, L. Hetey and K. Drescher, 1982, Action of antipsychotics on LSD-induced neurochemical and behavioural effects in rats, in: Advances in Pharmacology and Therapeutics II, Vol. 4, eds. H. Yoshida, Y. Hagihara and S. Enashi (Pergamon Press, Oxford and New York) p. 137.

Persson, S.-A. 1977, The effects of LSD and 2-bromo-LSD on the striatal dopa accumulation after decarboxylase inhibition in rats, European J. Pharmacol. 43, 73.

Pieri, L., H.H. Keller, W. Burkard and M. Da Prada, 1978, Effects of lisuride and LSD on cerebral monoamine systems and hallucinosis, Nature (London) 272, 278.

Starke, K. 1978, Presynaptic regulation of release in the central nervous system, in: The Release of Catecholamines from Adrenergic Neurons, ed. D.M. Paton (Pergamon Press, Oxford and New York) p. 143.

Taylor, K.M. and R. Lavery, 1969, The metabolism of tritiated dopamine in regions of the rat brain in vivo. I. The separation of catecholamines and their metabolites, J. Neurochem. 16, 1361.

Waldmeier, P.C. and L. Maître, 1977, Neurochemical investigations of the interaction of N,N-dimethyltryptamine with the dopaminergic system in rat brain, Psychopharmacology 52, 137.

Wilcoxon, F., 1947, Probability tables for individual comparisons by ranking methods, Biometrics 3, 119.