3108

Life Sciences, Vol. 23, pp. 523-526
Printed in the U.S.A.

Pergamon Press

LSD AND RELATED DRUGS AS DA ANTAGONISTS: RECEPTOR-MEDIATED EFFECTS ON THE SYNTHESIS AND TURNOVER OF DA

Sven-Åke Persson

Department of Pharmacology, University of Umeå,
S-901 87 Umeå, Sweden

We have earlier shown that d-lysergic acid diethylamide, LSD and its 2-bromo derivative, BOL like the dopamine (DA) antagonist haloperidol increased the rate of the in vivo tyrosine hydroxylation in the striatum measured as the accumulation of DOPA after decarboxylase inhibition.

Now we have found that several agents structurally similar to LSD increase the in vivo tyrosine hydroxylation in the striatum. Psilocybin (50 mg/kg i.p.) and N,N-dimethyltryptamine (50 mg/kg i.p.) caused a short-lasting increase of DOPA accumulation, while mescaline (10 - 100 mg/kg i.p.) did not increase the DOPA accumulation. A marked increase of DOPA accumulation was observed after the 5-hydroxytryptamine (5-HT) antagonist cyproheptadine. The effects of LSD and structurally related drugs on the DOPA accumulation in the striatum appear to be mediated via DA antagonism at receptor level. However, these agents may control the DOPA accumulation via other receptors than DA receptors e.g. 5-HT receptors. A control of DOPA accumulation via receptors other than DA receptors appears to be predominant after treatment with N,N-dimethyltryptamine or psilocybin.

LSD and its bromo derivative, BOL, have been shown to increase the in vivo tyrosine hydroxylation in the striatum measured as the accumulation of DOPA after inhibition of the neuronal decarboxylase (1, 2). Furthermore we have found that LSD and BOL increased the concentration of 3,4-dihydroxyphenylacetic acid (DOPAC) in the striatum (3). These findings, together with the observation that LSD and BOL antagonized the effect of the DA agonist apomorphine on the DOPA accumulation, suggest that LSD and BOL like the DA antagonist haloperidol block central DA receptors. However, LSD like the DA agonist apomorphine was found to inhibit the increased rate of DOPA accumulation seen after cerebral hemitranssection, treatment with gamma-butyrolactone or after treatment with reserpine. BOL lacked these effects (1). These findings suggest that LSD and BOL act at central DA receptors. Depending on the functional activity in the nigro-neostriatal pathway LSD seems to act as an agonist or an antagonist, partial agonist. BOL appears to have only antagonistic properties.

We have now studied whether drugs, which are structurally similar to LSD, also have effects, which could be ascribed to activity at central DA receptors.

0300-9653/78/0807-0523$02.00/0

The experiments were performed on male Sprague-Dawley rats. In vivo tyrosine hydroxylation was measured as the accumulation of DOPA after inhibition of the neuronal decarboxylase by 3-hydroxybenzyl hydrazine HCl (NSD 1015). This method was originally developed by Carlsson et al. (4). DOPA was isolated and determined spectrophotofluorimetrically (1, 5). In order to examine the effects of the various drugs at presynaptic DA receptors (autoreceptors) we used the method described by Roth et al. (6). Gamma-butyrolactone, GBL has been shown to inhibit the impulse flow in the nigro-neostriatal pathway. Thereby the neuronal feedback mechanism (7) is probably eliminated. Drugs, which counteract the effects of GBL have therefore been suggested to act at presynaptic DA receptors. This method has shown to be a useful tool in order to differ between drugs which have presynaptic effects and drugs, which lack presynaptic effects. In a few experiments the short-time accumulation of DOPAC was measured (8). Statistical significance of the results was assessed using the two-tailed student's t-test.

Results

N,N-dimethyltryptamine (50 mg/kg i.p.) and psilocybin (50 mg/kg i.p.) significantly increased the accumulation of DOPA (Table I).

Table I

Time after drug administration	Drug	Dose (mg/kg i.p.)	n	DOPA (ng/g ± S.E.M.)	Comparisons between the various treatments (p-values)
0.5 h	a) NaCl		9	982± 65	-
	b) N,N-dimethyltryptamine	50	6	1362±157	a-b < 0.025
	c) Psilocybin	50	3	1154± 69	a-c N.S.
	d) Mescaline	100	6	902± 99	a-d N.S.
	e) Cyproheptadine HCl	10	3	2245±290	a-e < 0.001
1.0 h	f) N,N-dimethyltryptamine	50	6	1007±145	a-f N.S.
	g) Psilocybin	50	3	1343±141	a-g < 0.025
	h) Mescaline	100	6	854± 58	a-h N.S.
	i) Cyproheptadine HCl	10	3	2139±205	a-i < 0.001
2.0 h	j) N,N-dimethyltryptamine	50	4	769±101	a-j N.S.
	k) Psilocybin	50	3	1246±150	a-k N.S.
	l) Mescaline	100	6	805± 49	a-l N.S.
	m) Cyproheptadine HCl	10	4	1524±109	a-m < 0.001

DOPA accumulation at various times after the administration of NaCl, N,N-dimethyltryptamine, psilocybin, mescaline or cyproheptadine HCl. NSD 1015 (100 mg/kg i.p.) was administered to all rats 20 min. before sacrifice.

The increase after N,N-dimethyltryptamine was observed after 0.5 h and persisted for about 1 h. The increased DOPA accumulation after

the administration of psilocybin appeared after 1 h and tended to last 1 h. Mescaline did not significantly change the accumulation of DOPA.

Cyproheptadine (50 mg/kg i.p.) markedly increased the accumulation of DOPA. This increased DOPA accumulation lasted for at least 2 h.

N,N-dimethyltryptamine significantly decreased the short-time accumulation of DOPAC, while psilocybin had no significant effect (Table II).

Table II

Drug	NaCl 0.9 %	N,N-dimethyl-tryptamine 50 mg/kg	Psilocybin 50 mg/kg
DOPAC ng/g ± S.E.M. (n)	1107 ± 27 (12)	260 ± 27 (4)	1135 ± 38 (4)
Comparison with the control (p-values)	-	< 0.001	N.S.

DOPAC levels in the striatum 30 min. after the administration of N,N-dimethyltryptamine, psilocybin or NaCl.

Haloperidol (0.5 mg/kg i.p.) strongly and cyproheptadine (10 mg/kg i.p.) weakly antagonized the decreasing effect of apomorphine on the accumulation of DOPA. Mescaline, N,N-dimethyltryptamine and psilocybin did not antagonize the effect of apomorphine on the DOPA accumulation.

As previously reported (1, 9) apomorphine and also LSD (1) inhibited the effect of GBL on the DOPA accumulation. Mescaline, N,N-dimethyltryptamine, psilocybin and cyproheptadine did not show this effect.

Preliminary results showed that cyproheptadine did not antagonize the inhibiting effect of apomorphine on the DOPA accumulation after treatment with GBL. However, cyproheptadine antagonized the effect of LSD, on the DOPA accumulation after GBL.

Discussion

The present study shows that N,N-dimethyltryptamine and psilocybin like LSD increased the accumulation of DOPA in the striatum. The effects of N,N-dimethyltryptamine and psilocybin were rather short-lasting and less pronounced than those reported after LSD (1), while mescaline did not significantly change the accumulation of DOPA. In analogy with the effect of haloperidol, an increased DOPA accumulation after N,N-dimethyltryptamine and psilocybin could be a result of pre- and/or postsynaptic DA receptor blockade (10). However, in contrast to haloperidol N,N-dimethyltryptamine and psilocybin did not increase the striatal DOPAC levels. Furthermore N,N-dimethyltryptamine and psilocybin did not antagonize the effect

of apomorphine in rats with an intact nigro-neostriatal pathway or in rats treated with GBL. Therefore the effects of N,N-dimethyltryptamine and psilocybin on the DOPA accumulation appear not to be mediated by DA receptor blockade.

Cyproheptadine has been shown to block central 5-HT receptors (11, 12). In the present study cyproheptadine was found to effectively increase the DOPA accumulation. Cyproheptadine also had a weak antagonizing effect in rats treated with apomorphine. This drug may therefore be a weak DA receptor blocker. However, the findings in GBL-treated rats suggest that cyproheptadine predominantly blocks other receptors than DA receptors i.e. LSD-sensitive receptors or 5-HT receptors.

The present study shows that agents structurally related to LSD increase the DA-synthesis in a central, predominantly dopaminergic pathway. The examined drugs appear to control the DA-synthesis in the striatum predominantly via receptors other than DA-receptors probably LSD-sensitive receptors or 5-HT receptors. However, cyproheptadine appears to have an effect on DA receptors comparable with, but weaker than the effects reported after treatment with LSD and BOL (1).

Acknowledgements

I wish to thank Miss Inger Johansson for skilful technical assistance and Merck, Sharp and Dohme, Rahway, N.J. for providing cyproheptadine HCl. This work was supported by the Faculty of Medicine, University of Umeå and Karl Oskar Hanssons fond för neurologiska sjukdomar.

References

1. S.-Å. PERSSON, Europ. J. Pharmacol. 43 73-83 (1977).
2. W. KEHR and W. SPECKENBACH, Naunyn-Schmiedeberg's Arch. Pharmacol. 301 163-169 (1978).
3. S.-Å. PERSSON, Life Sci. 20 1199-1206 (1977).
4. A. CARLSSON, J.N. DAVIS, W. KEHR, M. LINDQVIST and C.V. ATACK, Naunyn-Schmiedeberg's Arch. Pharmacol. 275 153-168 (1972).
5. W. KEHR, A. CARLSSON and M. LINDQVIST, Naunyn-Schmiedeberg's Arch. Pharmacol. 274 273-280 (1972).
6. J.R. WALTERS and R.H. ROTH, Naunyn-Schmiedeberg's Arch. Pharmacol. 296 5-14 (1976).
7. A. CARLSSON and M. LINDQVIST, Acta Pharmacol. et Toxicol. 20 140-144 (1963).
8. R.H. ROTH, L.C. MURRIN and J.R. WALTERS, Europ. J. Pharmacol. 36 163-171 (1976).
9. J.R. WALTERS and R.H. ROTH, J. Pharmacol. Exp. Ther. 191 82-91 (1974).
10. A. CARLSSON, in Pre- and postsynaptic receptors (E. Usdin and W. Bunney, Jr., eds.), pp. 49-65, Marcel Dekker, Inc., New York (1975).
11. S.J. CORNE, R.W. PICKERING and B.T. WARNER, Brit. J. Pharmacol. 20 106-120 (1963).
12. J. MAJ, J. SARNEK, V. KLIMEK and A. RAWLOW, Pharmacol. Biochem. Behav. 5 201-205 (1976).