European Journal of Pharmacology, 96 (1983) 151–154
Elsevier

Short communication

MESCALINE ELICITS BEHAVIORAL EFFECTS IN CATS BY AN ACTION AT BOTH SEROTONIN AND DOPAMINE RECEPTORS

MICHAEL E. TRULSON *, TERRIANN CRISP and LESLIE J. HENDERSON

Department of Pharmacology, Marshall University School of Medicine, Huntington, West Virginia 25704, U.S.A.

Received 15 August 1983, revised MS received 11 October 1983, accepted 13 October 1983

M.E. TRULSON, T. CRISP and L.J. HENDERSON, *Mescaline elicits behavioral effects in cats by an action at both serotonin and dopamine receptors*, European J. Pharmacol. 96 (1983) 151–154.

The characteristic behavioral effects of mescaline in cats were nearly completely blocked by pretreatment with low doses of either a specific serotonin antagonist (methysergide) or a dopamine specific antagonist (haloperidol). These blocking effects were not due to non-specific actions, since methysergide did not block the behavioral effects of apomorphine, and haloperidol did not block the behavioral effects of 5-methoxy-N,N-dimethyltryptamine. Thus, it appears that the behavioral effects of mescaline are dependent upon the simultaneous action of the drug at both serotonin and dopamine receptors.

5-Methoxy-N,N-dimethyltryptamine Methysergide Haloperidol Dopamine Serotonin Cats
Limb flicks Mescaline

1. Introduction

Mescaline has been postulated to exert its characteristic behavioral and psychological effects by means of an action upon the central serotonin system. Aghajanian et al. (1970) reported that a subgroup of serotonin-containing raphe cells were inhibited by mescaline in rats. Several years later, McCall and Aghajanian (1980) found that mescaline sensitizes post-synaptic serotonin receptors in the brainstem. Neurochemical studies of the effects of mescaline on the central serotonin system have yielded conflicting results. For example, Freedman et al. (1970) reported that low doses of mescaline decreased brain levels of 5-hydroxyindoleacetic acid (5HIAA), the major metabolite of serotonin, while high doses increased brain 5HIAA. Consistent with this high dose effect, Tilson and Sparber (1972) reported that mescaline increased the release and/or re-uptake of serotonin. On the other hand, Tonge and Leonard (1969) reported the opposite effect, i.e., mescaline was found to increase serotonin levels and decrease brain 5HIAA. In recent studies from our laboratory (Trulson et al., 1981) examining the effects of mescaline on the activity of serotonin-containing neurons in the nucleus raphe dorsalis and nucleus centralis superior, we found no overall change in raphe unit activity following administration of mescaline (5 mg/kg, i.p.); however, some individual units showed a significant increase in activity, while others showed a significant decrease, and still others showed no significant change in activity.

Other studies have concentrated on the dopaminergic effects of mescaline. This drug possesses a phenylethylamine moiety, and thus is a structural analog of amphetamine, a prototypic dopamine-releasing agent. Mescaline produces dopamine-related stereotyped behaviors in rodents and induces ipsilateral turning in rats with unilateral lesions of the nigro-striatal bundle (Trulson et al. 1977). Neurochemical studies also sup-

* To whom all correspondence should be addressed: Department of Pharmacology, Marshall University School of Medicine, 1542 Spring Valley Drive, Huntington, West Virginia 25704, U.S.A.

port the notion that mescaline is a modestly potent releaser of dopamine, both in vivo and in vitro (Costa and Garattini, 1970).

Since a considerable amount of evidence suggests that mescaline acts on both serotonin and dopamine neurons in the brain, we decided to examine the relative importance of these two actions in eliciting behavioral changes in cats. The cat is particularly well suited for this type of study because mescaline, LSD, and related drugs elicit a constellation of behavioral signs that can serve as a useful behavioral model for the actions of hallucinogens (Jacobs et al., 1977). Our data suggest that mescaline exerts its behavioral effects via a simultaneous action on *both* serotonin and dopamine receptors.

2. Materials and methods

Adult male (n = 4) and female (n = 6) cats weighing 2.4-3.3 kg were housed in standard stainless steel cat cages, which also served as the experimental observation chamber, in a room kept at constant temperature (22 ± 2°C) and on a 12 : 12 h light-dark cycle (lights on at 8:00 a.m.). The animals were habituated to the laboratory setting for 3 weeks before the experiments were initiated. Food, water and a litter pan were available during all experimental sessions. Using a counterbalanced design, each of the 10 cats received all of the drug combinations used. Cats were given intraperitoneal injections (except for 5MeODMT, which was given i.m.) of either saline (0.5 ml/kg), saline plus mescaline (5 mg/kg), methysergide (1 mg/kg) plus mescaline (5 mg/kg), haloperidol (0.5 mg/kg) plus mescaline (5 mg/kg), 5-methoxy-N,N-dimethyltryptamine (5MeODMT, 0.1 mg/ kg), methysergide (1 mg/kg) plus 5 MeODMT (0.1 mg/kg), haloperidol (0.5 mg/kg) plus 5MeODMT (0.1 mg/kg), saline plus apomorphine (4 mg/kg), methysergide (1 mg/kg) plus apomorphine (4 mg/kg), or haloperidol (0.5 mg/kg) plus apomorphine (4 mg/kg). All pretreatments were administered 20 min prior to the test drug (mescaline, 5MeODMT, or apomorphine). 5MeODMT was employed because it is a 'pure' serotonin agonist, virtually devoid of dopaminergic actions at the dose used; and apomorphine was used since it is a 'pure' dopamine agonist devoid of serotonergic effects at the dose used (Trulson and Crisp, 1982). One week intervened between consecutive sessions with the same cats.

After administration of the test drug, the cats were observed for one h by raters who were unaware of the treatment. The behavior was scored for limb flicking (lifting the forepaw or hindpaw and then rapidly snapping or flicking the limb outward from the body), abortive grooming (orienting to the body surface as if to groom, but not emitting the consummatory grooming bite, lick or scratch, or emitting such a response in midair), grooming (rubbing the head with the forepaw, licking and scratching the body surface), head shakes, staring (fixation of the gaze in one direction for more than 5 s), investigatory responses (pawing or sniffing at objects or in corners, chasing the tail, or batting at piecing of food, etc.), hallucinatory-like responses (looking around at the floor, ceiling or walls of the cage and appearing the track objects visually, or hissing at, batting at, or pouncing at 'unseen' objects), and yawning. The validity and reliability of this constellation of behavioral signs for studying the actions of hallucinogens has been discussed in our previous papers (e.g., Jacobs et al., 1977; Trulson and Crisp, 1982).

The data for each behavior was analyzed with an analysis of variance (ANOVA) for drug effect, using saline as a dose of 0. Comparisons between individual drug combinations were then made using Newman-Keuls tests.

3. Results

The data are summarized in table 1. An ANOVA revealed a significant drug effect ($P < 0.05$). Mescaline produced significant increases in limb flicking, abortive grooming, grooming, head shakes, stares, and hallucinatory-like responses, compared to saline baseline. Pretreatment with methysergide blocked all of these behavioral changes, with the exception of stares. Similarly, haloperidol pretreatment blocked all of the mescaline-induced behavioral changes as well (table 1). 5MeODMT also produced the characteristic be-

TABLE 1

Behavioral effects of mescaline, apomorphine and 5-methyoxy-N,N-dimethyltryptamine in cats. Cats were administered the above drug combinations and behavior was recorded for one h post-injection. Data are presented as mean hourly occurrences ± S.E.M. (n = 10 per group). [a] Significantly different from saline control value, $P < 0.05$, Newman-Keuls tests; [b] significantly different from saline plus corresponding test drug (mescaline, 5MeODMT, or apomorphine), $P < 0.05$, Newman-Keuls tests. Abbreviations: Flick, limb flicking; Abort, abortive grooming; Groom, functional grooming; Shakes, head shakes; Invest, investigatory responses; and halluc, hallucinatory-like responses.

Drug (dose, mg/kg)	Behavior							
	Flick	Abort	Groom	Shakes	Stares	Invest	Halluc	Yawn
Saline	0.2 ± 0.2	0.0 ± 0.0	6.3 ± 1.8	5.3 ± 2.3	0.9 ± 0.5	0.0 ± 0.0	0.0 ± 0.0	0.6 ± 0.2
Saline + mescaline (5)	27.3 ± 3.3 [a]	2.9 ± 0.3 [a]	13.8 ± 2.6 [a]	14.8 ± 3.8 [a]	7.4 ± 1.9 [a]	1.4 ± 0.4 [a]	1.8 ± 0.2 [a]	1.3 ± 0.4
Methysergide (1) + mescaline (5)	4.4 ± 2.8 [b]	0.1 ± 0.1 [b]	2.3 ± 0.9 [b]	3.8 ± 1.6 [b]	16.8 ± 6.2 [a,b]	0.5 ± 0.3	0.0 ± 0.0 [b]	1.1 ± 0.9
Haloperidol (0.5) + mescaline (5)	0.5 ± 0.4 [b]	0.5 ± 0.5 [b]	2.5 ± 1.8 [b]	2.3 ± 1.6 [b]	5.8 ± 2.7 [a]	0.0 ± 0.0	0.0 ± 0.0	0.5 ± 0.5
Saline + 5MeODMT (0.1)	18.5 ± 2.3 [a]	2.1 ± 0.6 [a]	8.3 ± 1.8	13.1 ± 1.8 [a]	10.1 ± 2.5 [a]	0.6 ± 0.3	0.3 ± 0.2	0.8 ± 0.2
Methysergide (1) + 5MeODMT (0.1)	4.0 ± 1.5 [b]	0.1 ± 0.1 [b]	1.5 ± 0.9 [a,b]	4.9 ± 1.7 [b]	4.1 ± 1.1 [b]	0.0 ± 0.0	0.0 ± 0.0	0.8 ± 0.5
Haloperidol (0.5) + 5MeODMT (0.1)	12.3 ± 2.8 [a]	1.1 ± 0.6	5.1 ± 0.3 [b]	3.5 ± 0.3 [b]	5.3 ± 1.9 [b]	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Saline + apomorphine (4)	23.9 ± 4.4 [a]	9.5 ± 5.6 [a]	19.6 ± 5.7 [a]	16.1 ± 5.4 [a]	16.1 ± 5.4 [a]	0.2 ± 0.2	0.5 ± 0.5	0.0 ± 0.0
Methysergide (1) + apomorphine (4)	27.4 ± 3.9 [a]	3.4 ± 1.4 [a]	13.8 ± 2.4 [a]	11.3 ± 1.7 [a]	10.8 ± 3.7 [a]	0.1 ± 0.1	0.0 ± 0.0	0.0 ± 0.0
Haloperidol (0.5) + apomorphine (4)	1.1 ± 0.3 [b]	0.0 ± 0.0 [b]	2.2 ± 0.5 [a,b]	2.0 ± 1.1 [b]	0.9 ± 0.4 [b]	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0

havioral syndrome in cats. The behavioral effects of 5MeODMT were blocked by pretreatment with methysergide, but not haloperidol (with the exception of a significant decrease in grooming) (table 1). Apomorphine elicited the characteristic behavioral changes as well (as previously reported, Trulson and Crisp, 1982), and the apomorphine-induced behavioral changes were totally blocked by haloperidol, but were not significantly altered by pretreatment with methysergide (table 1).

4. Discussion

The present data demonstrate that the behavioral effects of mescaline in cats are produced by an action of the drug at both serotonin and dopamine receptors. The behavioral syndrome following mescaline treatment was blocked both by a serotonin-specific receptor blocker (methysergide) as well as a dopamine-specific receptor antagonist (haloperidol). That the blocking effects of methysergide on mescaline-induced behaviors is not a non-specific effect of the drug pretreatment is indicated by the fact that methysergide did not block apomorphine-induced behavioral changes. In addition, we have previously reported that other serotonin-specific receptor blockers (cinnanserin, cyproheptidine) produced no significant changes in apomorphine-induced behaviors (Trulson and Crisp, 1982). Furthermore, the fact that the blocking effects of haloperidol on mescaline's action is not due to a non-specific effect is indicated by the observation that haloperidol did not block the actions of 5MeODMT.

Thus, it appears that mescaline exerts its behavioral effects in cats by an action at *both* serotonin and dopamine receptors. Moreover, an action at both sites simultaneously appears to be necessary, since pretreatment with either methysergide *or* haloperidol produces a nearly complete blockade of the behavioral effects of mescaline. The dose of mescaline employed in the present study was used because our prior studies indicated that lower doses were behaviorally ineffective, while higher doses were too toxic (Trulson et al., 1981). We have observed similar blocking actions by either methysergide or haloperidol of the behavioral effects of LSD, a drug which has also been demonstrated to have both serotonergic and dopaminergic properties (Aghajanian et al., 1970; Trulson et al., 1977).

In conclusion, the behavioral effects of mescaline in cats appears to depend upon a simultaneous agonist action at *both* serotonin and dopamine receptors. Preliminary data suggest that this may also be true for certain other indoleamine and phenylethylamine hallucinogens, such as LSD.

References

Aghajanian, G.K., W.E. Foote and M.H. Sheard, 1970, Action of psychotogenic drugs on midbrain raphe neurons, J. Pharmacol. Exp. Ther. 171, 178.

Costa, E. and S. Garattini, 1970, Amphetamines and Related Compounds, New York, Raven Press.

Freedman, D.X., R. Gottlieb and R.A. Lovell, 1970, Psychotomimetic drugs and brain 5-hydroxytryptamine metabolism, Biochem. Pharmacol. 19, 1181.

Jacobs, B.L., M.E. Trulson and W.C. Stern, 1977, Behavioral effects of LSD in the cat: Proposal of an animal behavioral model for studying the actions of hallucinogenic drugs, Brain Res. 132, 301.

McCall, R.B. and G.K. Aghajanian, 1980, Hallucinogens sensitize serotonin and norepinephrine receptors in the facial motor nucleus, Life Sci. 26, 1149.

Tilson, H.A. and S.B. Sparber, 1972, Studies on the concurrent behavioral and neurochemical effects of psychoactive drugs using the push-pull cannula, J. Pharmacol. Exp. Ther. 181, 387.

Tonge, S.R. and B.E. Leonard, 1969, The effects of some hallucinogenic drugs upon the metabolism of 5-hydroxytryptamine in brain, Life Sci. 8, 805.

Trulson, M.E. and T. Crisp, 1982, Behavioral and neurochemical effects of apomorphine in the cat, European J. Pharmacol. 78, 295.

Trulson, M.E., J. Heym and B.L. Jacobs, 1981, Dissociations between the effects of hallucinogenic drugs on behavior and raphe unit activity in freely moving cats, Brain Res. 215, 275.

Trulson, M.E., A.D. Stark and B.L. Jacobs, 1977, Comparative effects of hallucinogenic drugs on rotational behavior in rats with unilateral 6-hydroxydopamine lesions, European J. Pharmacol. 44, 113.