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Page 2, MK-486 was the study name for carbidopa

PARTICIPATION OF DOPAMINE- AND SEROTONIN-RECEPTORS IN THE DISAGGREGATION OF BRAIN POLYSOMES BY L-DOPA AND L-5-HTP

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Abstract—It has previously been shown that the disaggregation of brain polysomes and suppression of brain protein synthesis observed in rats given the amino acids L-dopa or L-5-HTP is mediated by the decarboxylation products dopamine and serotonin. Present studies demonstrate that the polysome disaggregation is caused by the interactions of the monoamines with specific receptor sites. Thus, dopa-induced disaggregation is blocked if rats are pretreated with haloperidol or pimozide (but not methysergide or cyproheptadine), while 5-HTP-induced disaggregation is blocked by methysergide or cyproheptadine (but not by haloperidol or pimozide).

Pretreatment of rats with MK-486, a drug that inhibits dopa decarboxylase in blood vessels and peripheral tissues but not brain, does not block dopa-induced brain polysome disaggregation; hence this disaggregation depends on the interaction of dopamine with receptors in the brain parenchyma. Brain polysomes are not disaggregated in rats given intraperitoneal apomorphine (or intracisternal dopamine). The disaggregation caused by dopa is not reduced in animals pretreated with sufficient intracisternal 6-hydroxydopamine to cause major damage to catecholaminergic nerve terminals.

BRAIN protein synthesis is transiently disrupted in animals treated with L-dihydroxyphenylalanine (dopa) or L-5-hydroxytryptophan (5-HTP), the amino acid precursors of the monoamine neurotransmitters dopamine and serotonin. Both amino acids disaggregate brain polysomes, and in both cases the disaggregation is mediated by the corresponding monoamine (WEISS *et al.*, 1971, 1972, 1973, 1974). The polysome disaggregation caused by dopa is temporally correlated with decreased *in vivo* incorporation of amino acids into brain proteins (MUNRO *et al.*, 1973; ROEL *et al.*, 1974). We now show that the changes in brain polysomes and protein synthesis induced by dopa and 5-HTP are mediated by pharmacologically-defined dopamine- and serotonin-receptors located within the brain parenchyma.

MATERIALS AND METHODS

Sprague–Dawley rats (Charles River CD, Wilmington, Mass.) were exposed to light (Vita-Lite, Duro-Test Co., North Bergen, N.J.) from 9 a.m. to 9 p.m. daily and given access to food (Big Red Rat Chow, Agway, Syracuse, N.Y.) and water *ad libitum*. Animals were decapitated at 1 p.m. Male rats weighing 50–75 g were used in all experiments except those with 6-hydroxydopamine. The drugs were administered intraperitoneally (i.p.). Suckling litters of both sexes received 6-hydroxydopamine intracisternally (i.c.) twice (on their day of birth and 2 days later) and were killed at weaning, 21 days after birth.

L-Dopa (Hoffmann–LaRoche, Nutley, N.J.) and L-5-hydroxytryptophan (Nutritional Biochemicals Corp., Cleveland, Ohio) were administered in 0·05 N-HCl. L-MK-486 (Merck Co., Rahway, N.J.) and 6-hydroxydopamine hydrobromide (Regis Chemical Co., Morton Grove, Ill.) were dissolved in 0·9% saline. Pimozide (McNeil Labs, Inc., Fort Washington, Pa.) was suspended in methyl cellulose. Haloperidol (McNeil Labs.) was dissolved in 0·05 N-citric acid. Methysergide bimaleate (Sandoz Pharmaceuticals, Hanover, N.J.) was dissolved in 0·9% saline. Cyproheptadine (HCl; Merck Co.) was dissolved in 0·05 N-HCl. Apomorphine HCl (Merck Co.) was dissolved in 0·9% saline.

Whole brain polysome profiles were prepared as previously described (WEISS *et al.*, 1971, 1972). Brain and heart dopa and dopamine levels were measured as described earlier (WEISS *et al.*, 1972) by modifications of the methods of VON EULER & LISHAJKO (1959) and CARLSSON & WALDECK (1958). Data were evaluated statistically by Student's *t*-test.

RESULTS

Mediation of polysome disaggregation by dopamine and serotonin receptors. It has previously been shown (WEISS *et al.*, 1972, 1973) that the disaggregation of brain polysomes following the administration of dopa or 5-HTP to rats is mediated by the monoamines, dopamine and serotonin. In order to determine whether the monoamines act on characteristic receptors for dopamine or serotonin, brain polysome aggregation was examined in rats given dopa or 5-HTP after drugs known to block these receptors.

Animals treated with the dopamine-receptor blockers pimozide or haloperidol, or the serotonin-receptor blockers methysergide or cyproheptidine,

Abbreviations used: L-dopa, L-3,4-dihydroxyphenylalanine; L-5-HTP, L-5-hydroxytryptophan; MK-486 L-α-methyl dopa hydrazine.

TABLE 1. EFFECTS OF BLOCKING DOPAMINE AND SEROTONIN RECEPTORS ON THE DISAGGREGATION OF BRAIN POLYSOMES BY L-DOPA AND L-5-HYDROXYTRYPTOPHAN

Vehicles		Dose (mg/kg)	Time (min)	Polysomes (% of profile)
0·05 N-HCl (L-dopa series)		—	60	71 ± 2·7 (6)
0·05 N-HCl (L-5-HTP series)		—	60	71 ± 2·2 (5)
Methyl cellulose		—	90	65 ± 1·4 (3)
0·05 N-Citric acid		—	90	69 ± 1·3 (3)
Inhibitors	Vehicle			
Pimozide	Methyl cellulose	25	90	68 ± 0·5 (4)
Haloperidol	0·05 N-Citric acid	20	90	65 ± 1·7 (3)
Methysergide	Saline	2	90	64 ± 3·2 (3)
Cyproheptadine	0·05 N-HCl	10	90	71 ± 2·5 (3)
L-Dopa and inhibitors				
L-Dopa alone	0·05 N-HCl	500	60	32 ± 3·0 (10)†
Pimozide	Methyl cellulose	25	90	66 ± 0·8 (3)
+ L-dopa	0·05 N-HCl	500	60	
Haloperidol	0·05 N-Citric acid	20	90	65 ± 1·7 (3)
+ L-dopa	0·05 N-HCl	500	60	
Methysergide	Saline	2	90	39 ± 4·8 (3)†
+ L-dopa	0·05 N-HCl	500	60	
Cyproheptadine	0·05 N-HCl	10	90	32 ± 6·8 (3)†
+ L-dopa	0·05 N-HCl	500	60	
L-5-HTP and inhibitors				
L-5-HTP alone	0·05 N-HCl	500	60	40 ± 2·8 (5)†
Pimozide	Methyl cellulose	25	90	41 ± 3·4 (3)†
+ L-5-HTP	0·05 N-HCl	500	60	
Haloperidol	0·05 N Citric acid	20	90	59 ± 3·1 (3)*
+ L-5-HTP	0·05 N-HCl	500	60	
Methysergide	Saline	2	90	63 ± 1·5 (3)
+ L-5-HTP	0·05 N-HCl	500	60	
Cyproheptadine	0·05 N-HCl	10	90	69 ± 0·8 (3)
+ L-5-HTP	0·05 N-HCl	500	60	

Rats were pretreated with a dopamine receptor blocker (pimozide or haloperidol), or a serotonin receptor blocker (methysergide or cyproheptadine) received dopa, HTP, or their diluents. The number of determinations for each group is given in parentheses.

* $P < 0·05$ differs from control group receiving 0·05 N-HCl.

† $P < 0·001$ differs from control group receiving 0·05 N-HCl.

exhibited no significant changes in brain polysome aggregation (Table 1). If such animals were subsequently treated with a dose of L-dopa sufficient to disaggregate brain polysomes, the polysomal effect was blocked by pimozide and haloperidol, but not methysergide or cyproheptadine. In contrast, methysergide and cyproheptadine, but not pimozide or haloperidol, protected the animals against the polysome disaggregation caused by 5-HTP (Table 1).

Localization of polysome-disaggregating dopamine receptors within the brain. In order to determine whether the receptors with which dopamine and serotonin interact to disaggregate brain polysomes are located within the brain parenchyma (i.e. not within blood vessels or in other peripheral tissues), L-dopa-induced polysome disaggregation was examined in animals pretreated with MK-486, a drug that inhibits the enzyme aromatic L-amino acid decarboxylase in blood vessels and peripheral tissues, but not in brain.

Administration of the decarboxylase inhibitor alone had no effect on peripheral (i.e. cardiac) dopa or dopamine levels, nor on brain polysome aggregation, but did slightly increase brain dopa (Table 2). Pretreatment of rats with this dose of MK-486 blocked the rise in cardiac dopamine that followed subsequent injection of dopa, indicating that peripheral decarboxylation had been very largely inhibited. In contrast, the decarboxylase inhibitor did not block the L-dopa-induced rise in brain dopamine, thereby demonstrating that it had not affected the decarboxylase enzyme in the brain. Dopa continued to disaggregate brain polysomes after MK-486 administration (Table 2). Hence the receptor with which dopamine interacts to produce this effect must reside within the brain itself.

Experimental dissociation of catecholaminergic terminals from dopa-induced polysome disaggregation. The dopamine receptors that mediate L-dopa-induced polysome disaggregation could be identical with the postsynaptic receptors at dopaminergic synapses;