of the (+)- and (—)-enantiomers of butaclamol on the increase in cyclic AMP elicited by 5 μM noradrenaline (approximate Ka value). As shown in Table 2, (+)-butaclamol inhibits the increase in cyclic AMP in a dose-dependent manner, having an IC50 of approximately 0·5 μM. (—)-Butaclamol was found to be a weak inhibitor of the noradrenaline stimulated rise in cyclic AMP, having an IC50 $>>10$ μM. Neither (+)- nor (—)-butaclamol, in concentrations from 0·1 to 50 μM, changed the basal concentration of the nucleotide.

The present results indicate that the blocking effect of butaclamol on the specific noradrenergic cyclic AMP generating system in slices of the limbic forebrain also resides in the (+)-enantiomer thus also demonstrating sterospecificity for central noradrenaline receptor blockade. The availabilty of a stereochemically specific antagonist of a central noradrenaline adenylate cyclase receptor should provide an important tool to further elucidate this system. Although the stereospecific blockade by butaclamol of limbic dopamine receptors is quantitatively more pronounced (Lippmann & others, 1975), the present results do nevertheless further support the view that blockade of noradrenergic receptors in the limbic system may also contribute to the pharmacologic and perhaps therapeutic action of antipsychotic drugs.

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A pharmacologic model of Huntington's chorea

R. E. DILL*, R. L. DORRIS, I. PHILLIPS-THONNARD, *Baylor College of Dentistry, Department of Microscopic Anatomy. 800 Hall Street, Dallas, Texas 75226, U.S.A.*

There are few animal models for Huntington's chorea, a hereditary disorder characterized by involuntary choreic movements and psychotic behavior (Bruyn, 1968). Most models for this disease are produced by the systemic administration of L-dopa to normal animals (Mones, 1973) or L-dopa in animals with lesions in the striatum (Sax, Butters & others 1973) or dopaminergic tracts (Ng, Gelhard & others, 1973). However, recent studies on the involuntary movements produced in animals by the intrastriatal (i.s.) injection of 3-methoxytyramine (3-MT) may lead to a useful model of the disease (Cools, 1972; Dill & Campbell, 1973; Furgeson, Dill & Dorris, 1976). The i.s. injection of 3-MT, a normal brain metabolite of dopamine, and mescaline both produced identical movement disorders in rats and squirrel monkeys (Dill & Campbell, 1973) leading the authors to speculate that 3-MT could be a factor in psychosis. Thus, the proposed 3-MT model could reflect both motor and behavioural aspects of the disease.

If 3-MT-induced movements can serve as a model for Huntington's chorea, they should respond to other drugs in a manner similar to the responses of the disease to these drugs. For example, L-dopa therapy is known to exacerbate the symptoms of Huntington's chorea (Klawans, 1970), while neuroleptic drugs are known to be beneficial (Whittier, 1973). Monoamine oxidase inhibitors (MAOIs) plus methionine loading, factors, which theoretically should increase brain concentrations of 3-MT, are known to exacerbate the symptoms of some psychotic states (Pollin, Cardon & Kety, 1961; Brune & Himwich, 1962; Park, Baldessarini & Kety, 1965). Thus, a study was made of the effects of L-dopa, a MAOI and three neuroleptic drugs on 3-MT-induced dyskinesias in rats.

Male albino rats (250–300 g) were permanently cannulated bilaterally with stainless steel cannulae in the neostriatum at stereotaxic co-ordinates A +7·8,

* Correspondence.

L 3·0 and V 1·5 mm according to Pellegrino & Cushman, (1967). Drugs were injected through these cannulae one week after surgery and subsequently at a rate of once per week. The injections were made by means of a micrometer-driven syringe connected to the cannula with polyethylene tubing. Drugs were injected in volumes of 2 to 4 μl in 10 to 20 s followed by a 2 μl flush of physiologic saline at a rate of 1 μl min^{-1}. Two to three days later, the cannulae were flushed again with 3 μl of saline to remove traces of injected drugs. The injection technique was as described by Dill, Nickey & Little (1968).

3-Methoxytyramine hydrochloride (Sigma) was unilaterally injected i.s. in 4 μl saline at 30 μg μl^{-1} and the resulting dyskinesias ranked as follows: one point was recorded for each different dyskinetic activity; two points for each 5 min of activity up to 20 min; and two points for each level of activity catagorized as mild, moderate, severe, or convulsive. The dyskinetic signs were: contralateral forelimb tremor or choreic movements, contralateral hindlimb movements, ipsilateral forelimb movements, chewing, grimacing, neck tremor, neck torsion, rearing, bilateral forelimb tremor, sialorrhea, and generalized convulsions. The maximum summed rank was 29 points. The latency from the time of injection to the first appearance of dyskinesia was also recorded.

One week later the same cannula site was injected with the same dose of 3-MT after the animal had been pretreated with the test drug. The resulting dyskinesias and latency were determined as outlined above. These matched pairs of rank data were compared statistically by the Wilcoxon matched pairs signed ranks test (Siegel, 1956). Differences between mean latency of various groups were compared by the *t*-test. The MAOI used was pheniprazine (Regis), 5 mg kg^{-1}, given i.p. 18–20 h before the 3-MT test. L-Dopa (Sigma), 100 mg kg^{-1}, was given i.p. 1 h before the 3-MT test. The three neuroleptics were given i.p. as follows: haloperidol (McNeil) 2 or 5 mg kg^{-1}, 2 h; trifluoperazine (Smith Kline and French), 20 mg kg^{-1}, 1 h; and clozapine (Sandoz), 10 mg kg^{-1}, 0·5 h before the 3-MT test. Phentolamine (Ciba), an α-adrenergic receptor blocking agent, was given i.p. at a dose of 45 mg kg^{-1} 45 min before the 3-MT test. Physiologic saline injected i.s. in a volume of 4 μl served as a control for the i.s. injections. Cannula placement was verified by histological examination of the brain.

Table 1. *Effects of neuroleptics on dyskinesias induced by intrastriatal 3-methoxytyramine.*

Drugs, routes of injections and amount	Ratio of response	Median dyskinesia rank	Latency (min) Mean ± s.e.
3-MT, i.s., 120 μg	10/14	13	13·5 ± 3·4
3-MT + Haloperidol, i.p., 5 mg kg^{-1}, 2 h	5/14	0[a]	12·0 ± 4·7
3-MT, i.s., 120 μg	8/9	13	10·1 ± 1·6
3-MT + Haloperidol, i.p., 2 mg kg^{-1}, 2 h	8/9	12	21·1 ± 2·6
3-MT, i.s., 120 μg	10/10	17	11·0 ± 1·23
3-MT + trifluoperazine, i.p., 20 mg kg^{-1}, 1 h	4/10	0[b]	9 3 ± 3·54
3-MT, i.s., 120 μg	10/10	17	11 0 ± 1·38
3-MT + clozapine, i.p., 10 mg kg^{-1}, 1/2 h	7/10	10[a]	13·4 ± 6·45

[a] $P = 0.025$ (one tailed test).
[b] $P < 0.005$ (one tailed test).
Ratio of Response—number of sites producing dyskinesia/number of sites injected.

Table 2. *Effects of phentolamine, L-dopa, pheniprazine and haloperidol on dyskinesias induced by intrastriatal injections.*

Drugs, route of injections and amount	Ratio of response	Median dyskinesia rank	Latency (min) Mean ± s.e.
3-MT, i.s., 120 μg	8/8	16	12·0 ± 1·78
3-MT, i.s. + phentolamine, i.p., 10 mg kg^{-1}, 45 min	8/8	16	12·8 ± 1·87
3-MT, i.s., 120 μg	7/12	7	11·3 ± 2·48
3-MT + L-dopa, i.p., 100 mg kg^{-1}, 1 h	12/12	16[a]	13·2 ± 2·30
Carbachol, i.s., 1 μg	12/14	19	0·7 ± 0·4
Carb. + haloperidol, i.p., 5 mg kg^{-1}, 2 h	13/14	24·3[b]	0·5 ±0·3
3-MT, i.s., 120 μg	8/9	13	10·1 ± 1·6
3-MT + pheniprazine, i.p., 5 mg kg^{-1}, 18 h	8/9	20[a]	16·1 ± 1·4[c]
Saline, i.s., 4 μl	0/23	0	

[a] $P < 0.01$ (one tailed test).
[b] $P = 0.02$ (two tailed test).
[c] $P < 0.01$ (two tailed test).
Ratio of Response—number of sites producing dyskinesia/number of sites injected.

All three of the neuroleptics inhibited the effects of 3-MT, but at rather high dose levels (Table 1). This may indicate that the 3-MT, effect is mediated via the D2 dopamine receptor (Costall & Naylor, 1975). The suggestion that a dopamine receptor mediates the 3-MT effect is supported by the fact that phentolamine did not reduce the effects of 3-MT (Table 2).

Since haloperidol and trifluoperazine produced catalepsy and marked sedation at doses which reduced the 3-MT effects, it was deemed necessary to test the effects of catalepsy and sedation *per se* on similar dyskinesias induced by cholinergic stimulation of the striatum. Thus, one group of rats was injected i.s. with 1 μg carbachol (carbamylcholine chloride) (Sigma) and the resulting dyskinesias ranked as before. One week later, these animals were pretreated with 5 mg kg^{-1} haloperidol (i.p.) and 2 h later injected with carbachol as before. Carbachol-induced dyskinesias were superimposed on the haloperidol-induced catalepsy, i.e., tremors and involuntary movements continued to occur at an even greater intensity and duration (Table 2). Additionally, clozapine did not induce catalepsy but effectively reduced the effects of 3-MT (Table 1). Thus, the reduced spontaneous locomotor activity seen in neuroleptic-treated rats does not seem to be a major factor in the inhibitory effects of these drugs on 3-MT-induced dyskinesias.

Pheniprazine pretreatment significantly enhanced the 3-MT-induced dyskinesias (Table 2), suggesting that 3-MT was the active substance since its metabolism to homovanillic acid would be expected to be reduced. This was borne out by the observation that the mean duration of the 3-MT-induced activity increased from 22 to 87 min after pheniprazine pretreatment. Furthermore, a previous study (Dill, 1972) showed that the i.s.

injection of large amounts of homovanillic acid produced no effect. It is difficult to explain the increase in latency in the pheniprazine-treated rats (Table 2) unless a compensatory mechanism has developed in response to the increased endogenous 3-MT produced as a result of MAO inhibition.

L-Dopa also increased the 3-MT effect (Table 2). L-Dopa may also be expected to increase brain concentrations of 3-MT since much of it is converted to 3-*O*-methyldopa (Bartholini & Pletscher, 1968; Kuruma, Bartholini & Pletscher, 1970; Muenter, Sharpless & Tyce, 1972), which can be decarboxylated directly to 3-MT (Bartholini, Kuruma & Pletscher, 1972). Some of the L-dopa is metabolized to dopamine, which has been shown to potentiate the dyskinesia-inducing properties of 3-MT (Furgeson & others, 1976). Dopamine does not appear to be directly responsible for dyskinesias since inhibition of catechol-*O*-methyl transferase blocks the ability of i.s. dopamine to induce dyskinesias (Furgeson & others, 1976).

The induction of involuntary movements in rats by the i.s. injection of drugs is not unique. Cholinergic stimulation of this area with carbachol or acetylcholine produced dyskinesias (Dill & others, 1968), while McKenzie & Viik (1975) have induced similar movements in rats with i.s. injection of picrotoxin and (+)-tubocurarine. The effect of picrotoxin is of interest in that it is an inhibitor of GABA receptors and GABA is known to be reduced in the post-mortem brains of patients with Huntington's chorea (Perry, Hansen & Kloster, 1973).

However there is a strong implication of some disturbance of the dopaminergic system in this disease. Barbeau, 1973, has reviewed the literature on this subject which can be summarized as follows: (1) striatal dopamine concentrations are normal; (2) dopamine receptor blocking drugs are effective therapeutic agents; (3) reserpine is beneficial; (4) α-methyl-*p*-tyrosine is beneficial; (5) in some cases α-methyldopa has been found to be beneficial; and (6) L-dopa exacerbates the symptoms. Cools (1971) has shown that α-methyl-*p*-tyrosine blocks the dyskinesia-inducing property of i.s. administered 3-MT in cats. Thus, there is a close parallel between the drug response of the i.s. 3-MT model of Huntington's chorea and the disease in man. It should also be pointed out that a parallel exists between the drug response of this model and the response of schizophrenic patients to L-dopa, MAOIs and neuroleptics (Klawans, Goetz & Westheimer, 1972).

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