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INTERACTION OF APOMORPHINE, NEUROLEPTICS AND STIMULANTS WITH α-METHYL-*m*-TYRAMINE, A FALSE DOPAMINERGIC TRANSMITTER*

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Abstract—The rate of decline of α-methyl-*m*-tyramine (MMTA) from the corpus striatum of the rat can be altered by drugs acting on the dopamine (DA) receptor. By the use of this false dopaminergic transmitter, amine release by drugs acting directly on the neurone can be distinguished from that by drugs acting indirectly via DA receptor interaction. The rate of disappearance of MMTA is much slower than that of DA after tyrosine hydroxylase inhibition, but the combination of synthesis blockade and monoamine oxidase blockade greatly slowed the rate of DA decline, suggesting that normally much DA is metabolized intraneuronally. The decline rate of MMTA appears to accurately reflect the striatal DA neurone impulse flow rate under normal conditions or after administration of drugs which act only to alter impulse flow.

AFTER administration of α-methyl-*m*-tyrosine (αMMT), its decarboxylated product, α-methyl-*m*-tyramine (MMTA), accumulates specifically in the corpus striatum of rats and rabbits along with a lowering of dopamine (DA) content in that brain region, while metaraminol, the β-hydroxylated product of MMTA, accumulates specifically in norepinephrine-rich areas of the brain (e.g. hypothalamus) along with a lowering of the norepinephrine content in those areas.[1] The specific localization of the dopamine analog, MMTA, in a dopamine-rich area of the brain and its release by *d*-amphetamine,[2] a drug which releases DA,[3] suggests that MMTA acts as a false dopaminergic transmitter which may be used as a model nonmetabolizable amine in the study of central dopaminergic mechanisms.

Consistent with this possibility we reported[4] that apomorphine, a direct DA receptor agonist which reduces DA turnover by reflexly decreasing impulse flow in striatal DA neurons,[5] also attenuates the disappearance of MMTA from rat striatum, while haloperidol, which reflexly increases DA turnover by blocking DA receptors,[6] enhances the disappearance of MMTA from rat striatum. The lowering of MMTA by haloperidol was inhibited by simultaneous treatment with apomorphine, an interaction similar to that of the two drugs on striatal DA content.[5] The present paper is an extension of that study and provides evidence suggesting that the rate of decline of striatal MMTA content in the rat parallels the rate of impulse flow under normal conditions or after drugs which act only to alter impulse flow. The results also demonstrate that the mechanisms of various drugs such as neuroleptics and central stimulants acting on the striatum can be partly differentiated by their actions on striatal MMTA and their interaction with apomorphine.

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METHODS

Female Sprague–Dawley rats (200–250 g) were used throughout the study. DLαMMT (100 mg/kg) was administered subcutaneously. Animals were killed by chloroform asphyxiation, brains removed, chilled in ice-cold saline, and the striata removed.[7] Striatal MMTA concentrations were measured as described previously.[1,8] Striatal dopamine was measured by the method of Neff and Costa[9] at various times after administration of the tyrosine hydroxylase inhibitor, DLα-methyltyrosine (αMT) (200 mg/kg, i.p., +100 mg/kg at 2-hr intervals), some rats also having received the monoamine oxidase (MAO) inhibitor, pheniprazine (5 mg/kg, i.p.) 30 min before αMT.

RESULTS

Effects of various doses of neuroleptics on rat striatal MMTA concentration. Figure 1 shows the depletion of rat striatal MMTA content 6 hr after administration of various doses of haloperidol or trifluoperazine. The rate of depletion was maximal with a dose of haloperidol of 0·5 mg/kg or trifluoperazine at a dose of 2 mg/kg. The dose of trifluoperazine required to produce about one-half the maximal depletion was almost 10 times that of haloperidol, yet both drugs produced the same maximal effect, suggesting saturation of the dopamine receptor by large doses of either neuroleptic.

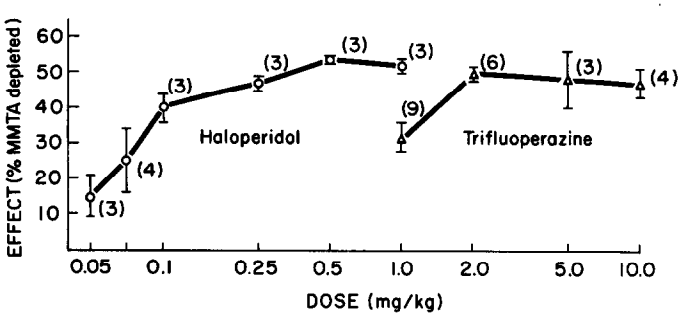

FIG. 1. Effect of various doses of haloperidol or trifluoperazine on MMTA content of rat striatum. Rats were given DLαMMT (100 mg/kg, s.c.) and neuroleptics, i.p., 17 hr later. The animals were killed after a further 6 hr. Shown are number of experiments and standard errors.

Effects of various doses of central stimulants on rat striatal MMTA concentration. Figure 2 shows the depletion of striatal MMTA 3 hr after treatment with various doses of amfonelic acid or *d*-amphetamine sulfate. Maximal depletion of MMTA was attained with about 5 mg/kg amphetamine sulfate, whereas no maximum was observed over the dose range used for amfonelic acid.

Antagonism by apomorphine of the effect of neuroleptics on rat striatal MMTA. The normal decline of striatal MMTA during the interval between 17 and 23 hr after αMMT administration was blocked by apomorphine treatment (Table 1). A low submaximally effective dose of haloperidol, 0·1 mg/kg, i.p., markedly accelerated the rate of decline of MMTA from the striatum, but this effect was completely blocked by apomorphine administration. A similar blocking effect of apomorphine was seen on the depletion of MMTA by a submaximally effective dose of trifluoperazine (Table 1).

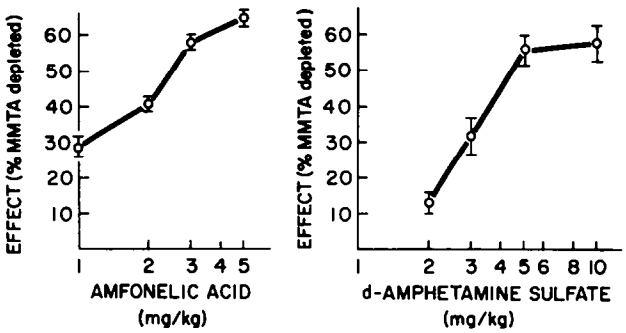

FIG. 2. Effect of various doses of amfonelic acid or *d*-amphetamine on MMTA content of rat striatum. Rats were given DL-αMMT (100 mg/kg, s.c.) and the stimulants, i.p., 18 hr later. The animals were killed after a further 3 hr. Shown are numbers of experiments and standard errors.

Release of rat striatal MMTA by d-amphetamine or amfonelic acid in the presence of apomorphine. The small control decline (15 per cent) of MMTA during the interval between 18 and 21 hr was markedly increased by a submaximally effective dose of *d*-amphetamine (3 mg/kg) or amfonelic acid (2 mg/kg) to 42 and 51 per cent respectively (Table 2). In contrast to its pronounced blocking action against the neuroleptics, apomorphine had little or no effect on the action of the central stimulants on MMTA content.

TABLE 1. EFFECT OF APOMORPHINE, NEUROLEPTICS AND COMBINATION OF APOMORPHINE AND NEUROLEPTICS ON RAT STRIATAL MMTA CONCENTRATION*

	Treatment	Striatal MMTA (μg/g ± S.E.)	MMTA released by neuroleptics (μg/g)
A	αMMT, 17 hr	0·75 ± 0·03 (8)	
B	αMMT, 23 hr	0·55 ± 0·01† (27)	
C	αMMT, 23 hr, +apomorphine	0·70 ± 0·04‡ (4)	
D	αMMT, 23 hr, +haloperidol	0·38 ± 0·00§ (13)	0·17 (B minus D)
E	αMMT, 23 hr, +apomorphine +haloperidol	0·70 ± 0·03‡,‖ (4)	0·00 (C minus E)
F	αMMT, 23 hr, +trifluoperazine	0·36 ± 0·05§ (6)	0·19 (B minus E)
G	αMMT, 23 hr, +apomorphine +trifluoperazine	0·66 ± 0·03¶ (6)	0·04 (C minus G)

* Apomorphine (2 mg/kg, s.c., hourly), haloperidol (0·1 mg/kg, i.p.) and trifluoperazine (1·0 mg/kg, i.p.) were administered 17 hr after DL-αMMT (100 mg/kg, s.c.) and animals killed 6 hr later. When apomorphine was given in combination with another drug, the other drug was administered 5 min before the first apomorphine injection. Figures in parentheses denote number of experiments.

† Significant difference from 17-hr control ($P < 0·0005$).
‡ No significant difference from 17-hr control.
§ Significant difference from 23-hr control ($P < 0·0005$).
‖ Significant difference from treatment D ($P < 0·0005$).
¶ Significant difference from treatment F ($P < 0·0005$).

TABLE 2. EFFECT OF *d*-AMPHETAMINE, AMFONELIC ACID OR APOMORPHINE OR COMBINATION OF *d*-AMPHETAMINE OR AMFONELIC ACID AND APOMORPHINE ON RAT STRIATAL MMTA CONCENTRATION*

	Treatment	Striatal MMTA (μg/g ± S.E.)	MMTA released by *d*-amphetamine or amfonelic acid (μg/g)
A	αMMT, 18 hr	0·74 ± 0·04 (4)	
B	αMMT, 21 hr	0·63 ± 0·02† (4)	
C	αMMT, 21 hr +apomorphine	0·73 ± 0·05‡ (4)	
D	αMMT, 21 hr, +*d*-amphetamine	0·43 ± 0·03§ (4)	0·20 (B minus D)
E	αMMT, 21 hr, +apomorphine +*d*-amphetamine	0·58 ± 0·03‖ (4)	0·15 (C minus E)
F	αMMT, 21 hr, +amfonelic acid	0·36 ± 0·02¶ (4)	0·27 (B minus F)
G	αMMT, 21 hr, +apomorphine +amfonelic acid	0·44 ± 0·01** (4)	0·29 (C minus G)

* Apomorphine (2 mg/kg, s.c., hourly), *d*-amphetamine sulfate (3 mg/kg, i.p.) and amfonelic acid (2 mg/kg, i.p.) were administered 18 hr after DLαMMT (100 ng/kg, s.c.) and animals killed 3 hr later. When apomorphine was given in combination with another drug, the other drug was administered 5 min before the first apomorphine injection. Figures in parentheses denote number of experiments.

† Significant difference from 18-hr control ($P < 0·05$).

‡ No significant difference from 18-hr control.

§ Significant difference from 21-hr control ($P < 0·025$).

‖ Significant difference from treatment C ($P < 0·025$).

¶ Significant difference from 21-hr control ($P < 0·0005$).

** Significant difference from treatment C ($P < 0·0025$).

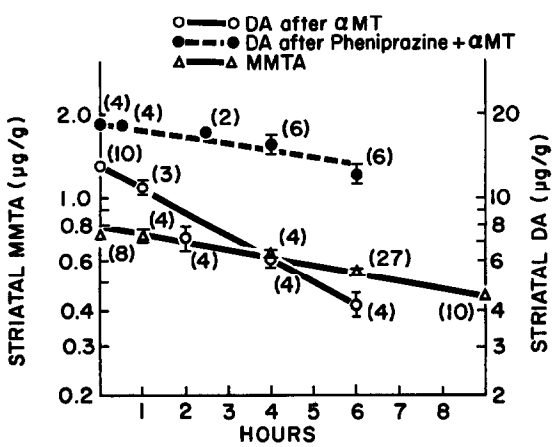

FIG. 3. Decline of rat striatal MMTA or of striatal DA after synthesis blockade with and without monoamine oxidase inhibition. Some rats were given DLαMMT and MMTA content was measured. Zero time on the graph is 17 hr after αMMT. Other rats were given αMT (200 mg/kg, i.p., plus 100 mg/kg at 2-hr intervals). Other αMT-treated rats received pheniprazine (5 mg/kg, i.p.) 30 min before αMT. Zero time is the time of αMT administration. Shown are numbers of experiments and standard errors.

Comparison of MMTA and DA half-times in striatum. Figure 3 shows the decline of DA from the striatum of αMT-treated rats and the effect of MAO blockade. Also shown is the decline of MMTA during the interval from 17 to 26 hr after treatment with αMMT. The estimated half-time of DA disappearance after synthesis inhibition was about 3·5 hr, while in the added presence of pheniprazine, it was about 12 hr.

DISCUSSION

The studies described in the present paper further point up the false dopaminergic function of MMTA and its usefulness as a tool to study drugs which affect dopaminergic neurons. Thus, the depletion of striatal MMTA by *d*-amphetamine, amfonelic acid and the two neuroleptics, haloperidol and trifluoperazine, is in agreement with the effect of these drugs on striatal DA.[3,6,10,11,*]

The antagonism by apomorphine of the depletion of MMTA by haloperidol was seen to be complete in the present study. In an earlier study[4] using a different dosage regimen, the effect of haloperidol was only partially overcome by apomorphine. In the present study using a submaximally effective dose of haloperidol, it could be seen that apomorphine could completely antagonize neuroleptic-induced MMTA depletion. These findings serve as further evidence that haloperidol and apomorphine modify the rate of striatal amine release by alteration of the degree of impulse flow via their opposing actions on the dopamine receptor.

While the neuroleptics thus enhance depletion indirectly, *d*-amphetamine and amfonelic acid are known to release DA directly from dopamine-containing nerve endings.[3,11,*] Thus, the net-releasing effect of these drugs should not be altered by receptor stimulation by apomorphine, especially in light of evidence that amphetamine also decreases the firing rate of the striatal neurone.[12] Consistent with this view was the finding that apomorphine had little or no effect on the release of MMTA by the stimulants. Thus, with this model it is possible to readily distinguish drugs which release transmitter amine by direct action at nerve endings from those which induce release reflexly as a result of receptor blockade.

It is interesting to note that while the rate of decline of brain DA after synthesis blockade is much faster than is the normal rate of MMTA decline, the superimposition of a MAO blocker markedly slows the rate of DA decline, indicating that normally much striatal DA is metabolized intraneuronally. The results suggest that the rate of striatal MMTA decline in the rat provides a measure of nigro-striatal impulse flow under normal conditions or after drugs which act only to alter impulse flow, a measure that is even more accurate than can be estimated by the kinetics of DA disappearance after synthesis blockade.

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