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N-METHYL-α-METHYL-TRYPTAMINE: A POTENT MONOAMINE OXIDASE INHIBITOR AND TRYPTAMINE ANTAGONIST

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Abstract—N-methyl-α-methyl-tryptamine is an inhibitor of monoamine oxidase (MAO) *in vivo*, as well as a tryptamine antagonist. At relatively low doses it enhances the effects of tryptamine by virtue of its inhibitory activity on MAO. This action is reversed at relatively high doses presumably because it competes with tryptamine for activation of receptor sites.

POTENTIATION of the convulsant effects of tryptamine has provided a useful method for testing for inhibition of monoamine oxidase (MAO) in intact animals.[1, 2] In the process of evaluating a series of compounds structurally related to tryptamine for inhibitory activity on MAO, it was observed that N-methyl-α-methyl tryptamine (SK & F 7024) potentiated tryptamine at relatively low doses but not at higher doses. This report is concerned with the study of this compound and of the mechanisms involved in its interaction with MAO.

METHODS

Monoamine oxidase inhibition of SK&F 7024 was measured *in vivo* by one biochemical and two pharmacological procedures. In all three, SK&F 7024 was administered orally and tested 1 hr later. This was found to be the time of peak drug effect by each of the procedures investigated.

(1) Tryptamine potentiation test.[1] Groups of rats were first treated with various doses of the drug under investigation and later, at the time of peak drug effect, all rats were injected intravenously with tryptamine, hydrochloride, 5 mg/kg. This dose of tryptamine causes convulsions in only 4% of untreated rats and is referred to as a CD_4. The dose of a drug effective in causing 50% of rats to respond to the CD_4 of tryptamine with 3 sec or more of uninterrupted clonic seizure activity (ED_{50}) and 95% fiducial limits was calculated according to the log-probit method of Litchfield and Wilcoxon.[3]

(2) 5-Hydroxytryptophane potentiation test. The procedure is essentially the same as that described for tryptamine potentiation except that 55 mg/kg of 5-hydroxytryptophane (5-HTP) is administered intravenously, instead of tryptamine. The ED_{50} is defined as the dose of drug effective in causing 50% of rats to respond to this dose of 5-HTP with 5 sec or more of uninterrupted clonic seizure activity during the 15-min

period following its administration. The data were analyzed by the graphic log-probit method of Litchfield and Wilcoxon.[3]

(3) Inhibition of 5-hydroxytryptamine (5-HT) disappearance (*in vivo*).* SK&F 7024 was administered to groups of rats in doses of 5, 10, 20, and 30 mg/kg. The animals were sacrificed by decapitation 1 hr later. The brains were removed immediately, rinsed free of adhering blood, lightly blotted, and weighed. Each brain was homogenized in 2 volumes of cold deionized water, and the MAO activity was assayed according to the method of Sjoerdsma *et al.*[4] The activity of MAO in brains of rats treated orally with the drug was compared with the enzyme activity of normal untreated rats, and the results calculated as per cent inhibition.

RESULTS

A summary of the results obtained is presented in Table 1. SK&F 7024 produced graded potentiation of tryptamine in doses up to 6 mg/kg, but effected less potentiation at 20 mg/kg and no potentiation at 25 or 30 mg/kg. In contrast, linear dose-response curves were obtained in the 5-HTP potentiation test and in the 5-HT disappearance test.

TABLE 1. ACTIVITY OF SK&F 7024 IN POTENTIATING TRYPTAMINE AND 5-HTP AND IN PREVENTING DISAPPEARANCE OF 5-HT

Procedure	Dose (mg/kg, oral)	Effect	ED_{50}* (mg/kg)
		% Potentiation	
Tryptamine potentiation	1·5	33	
	3·0	40	
	6·0	50	
	10·0	50	
	20·0	33	
	25·0	0	
	30·0	0	
		% Potentiation	
5-HTP potentiation	1·5	12·5	
	3·0	50·0	
	6·0	62·5	3·5
	12·0	100·0	
	20·0	100·0	
		% Inhibition MAO	
Prevention of 5-HT disappearance	5·0	25·8	
	10·0	46·7	
	20·0	57·5	12·0
	30·0	71·9	

* See Methods for definition.

The lack of potentiating activity of tryptamine at the higher doses of SK&F 7024 prompted us to test the compound for its effect on the threshold for tryptamine convulsions. A group of 160 rats was randomly divided into four groups of 40 rats each.

* In separate *in vitro*-experiments the concentration of drug necessary to inhibit the MAO activity of a normal brain homogenate by 50% (I_{50}) was determined by the method of Sjoerdsma *et al.*[4] The I_{50} for SK & F 7024 was approximately $4{\cdot}7 \times 10^{-6}$ M. Comparable values of I_{50}'s for iproniazid and tranylcypromine were $8{\cdot}7 \times 10^{-4}$ M and $9{\cdot}7 \times 10^{-7}$ M, respectively.

Groups I, II, and III were treated orally with 6, 25, and 30 mg/kg of SK&F 7024, respectively, and 1 hr later injected with various doses of tryptamine. The fourth group was first treated orally with equivalent volumes of water; various doses of tryptamine were injected intravenously 1 hr later. The percentage of rats responding to the tryptamine with 3 sec or more of uninterrupted clonic seizure activity was plotted against the logarithm of the dose of tryptamine and regression lines fitted graphically to the points. These curves are illustrated in Fig. 1. The dose of tryptamine effective

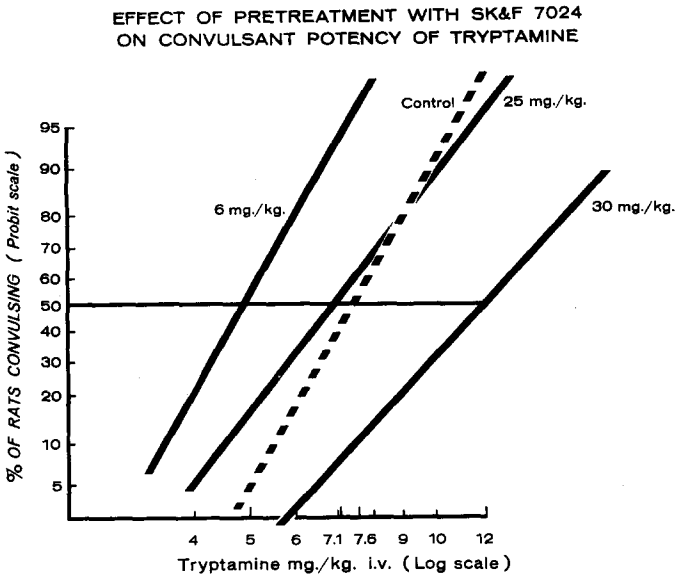

FIG. 1. Effect of oral pretreatment with SK & F 7024 on the convulsant dose-response curves for tryptamine administered intravenously to rats. See text for discussion.

in causing 50% of *control* rats to respond with 3 sec or more of uninterrupted clonic seizure activity (CD_{50}) was 7·6 (6·5–8·9) mg/kg. The corresponding CD_{50}'s for rats pretreated with 6, 25, and 30 mg/kg of SK&F 7024 were 5 (3·9–6·3), 7·1 (5·3–9·4), and 12 (10·0–14·7) mg/kg, respectively. The slopes of these regression lines do not deviate significantly from parallelism ($P > 0{\cdot}05$). Statistical analysis of these data indicates that rats pretreated with 6 mg/kg of SK&F 7024 required significantly *less* tryptamine to induce convulsions that did control animals ($P < 0{\cdot}05$). Rats pretreated with 25 mg/kg required essentially the same dose of tryptamine as did control animals, and rats pretreated with 30 mg/kg of SK&F 7024 required significantly *more* tryptamine to induce convulsions than did control animals ($P < 0{\cdot}05$).

DISCUSSION

SK&F 7024 apparently possesses a dual component of action involving both inhibition of MAO and blockade of serotonin/tryptamine receptors in brain. The inhibitory activity of the drug on MAO is clearly revealed by the fact that it prevents the disappearance of 5-HT, potentiates 5-HTP, and potentiates tryptamine at low doses. The latter action is clearly illustrated in Fig. 1, where an oral dose of 6 mg/kg

of SK&F 7024 significantly reduced the amount of tryptamine required to evoke convulsions. This potentiation of tryptamine may be explained by the fact that SK&F 7024 has inhibited MAO and thereby interfered with the rapid oxidation of tryptamine to indoleacetic acid.[1, 5] Consequently, less tryptamine is required to evoke convulsions, and the regression line is shifted to the left.

Although a relatively low dose of SK&F 7024 potentiated tryptamine, a dose of 30 mg/kg actually antagonized its convulsant action. As shown in Fig. 1, significantly more tryptamine was required to evoke convulsions in rats treated with 30 mg/kg of SK&F 7024 than was required in control animals. This action of SK&F 7024 is presumably due to a blocking effect at the receptor level. The character of the blocking effect appears to be both surmountable and competitive, because a sufficient increase in the dose of tryptamine is effective in overriding the blockade. The fact that the regression line for tryptamine in the presence of the antagonist does not deviate significantly from parallelism with the regression line for tryptamine in normal animals ($P > 0{\cdot}05$) is presumptive evidence that at this dose-level the nature of the antagonism is competitive.

Convulsions induced by 5-HTP in the presence of an MAO inhibitor are referable to the 5-HT formed by decarboxylation of 5-HTP rather than to the 5-HTP *per se*. Evidence in support of this conclusion has been presented elsewhere and need not be repeated here.[1] The uniqueness and striking similarity of convulsions evoked by both tryptamine and 5-HT (from 5-HTP) are taken as presumptive evidence that both substances activate similar receptor sites in the central nervous system. Although SK&F 7024 was effective in antagonizing convulsions induced by tryptamine, it failed to prevent convulsions induced by the 5-HT formed from 5-HTP. As shown in Table 1, SK&F 7024 effected a graded potentiation of 5-HTP, with doses of both 12 and 20 mg/kg of SK&F 7024 effecting 100% potentiation. It is postulated that the mechanism of this separation (*i.e.*, blockade by SK&F 7024 of tryptamine but not of 5-HT) involves the relative affinities of the three substances, 5-HT, SK&F 7024, and tryptamine for the receptor. It is suggested that 5-HT has the greatest affinity for the receptor and is capable of displacing SK&F 7024 regardless of its concentration at the receptor site. Consequently, the only effect seen with increasing doses of SK&F 7024 is a graded increase in the degree of potentiation of 5-HTP owing to increasing inhibition of MAO activity.

In the case of tryptamine, however, the situation is somewhat different. It is presumed that SK&F 7024 and tryptamine have an approximately equal affinity for the receptor site and that the final effect—antagonism or potentiation of tryptamine—is dependent upon the laws of mass action. At relatively low doses of SK&F 7024 (6 mg/kg) tryptamine is spared from oxidation by the inhibitory action of SK&F 7024 on MAO. At the same time, insufficient SK&F 7024 is present to prevent tryptamine from activating receptor sites, and potentiation of tryptamine's convulsant action occurs. Increasing the dose of SK&F 7024 to 25 mg/kg effects a sufficient increase in its concentration at the receptor site to balance the increased concentration of tryptamine at the receptor site so that neither potentiation nor antagonism of tryptamine's convulsant effect would be expected. Evidence in support of this conclusion is the fact that the regression line (Fig. 1) for tryptamine convulsions in animals pretreated with SK&F 7024 (25 mg/kg) is essentially indistinguishable from the regression line for tryptamine administered to control animals. Finally, at a dose of 30 mg/kg of

SK&F 7024, the balance is shifted to the right, in that sufficient antagonist is present to interfere with the activation of receptors by the elevated tryptamine levels, and the effect of tryptamine is actually antagonized. Increasing the dose of tryptamine is effective in breaking through the blockade, however and, as shown in the figure, the regression line for tryptamine convulsions at this point is shifted to the right.

REFERENCES

1. D. H. TEDESCHI, R. E. TEDESCHI and E. J. FELLOWS, *J. Pharmacol. exp. Ther.* **126**, 223 (1959).
2. D. H. TEDESCHI, R. E. TEDESCHI and E. J. FELLOWS, *Proc. Soc. exp. Biol. N. Y.* **103**, 680 (1960).
3. J. T. LITCHFIELD, JR. and F. WILCOXON, *J. Pharmacol. exp. Ther.* **96**, 99 (1949).
4. A. SJOERDSMA, T. E. SMITH, T. D. STEVENSON and S. UDENFRIEND, *Proc. Soc. exp. Biol. N. Y.* **89**, 36 (1955).
5. H. GREEN and J. L. SAWYER, *Proc. Soc. exp. Biol. N. Y.* **104**, 153 (1960).