Summary. Mice subjected to sound stress or a combination of avoidance-learning stress and sound stress showed a highly significant decrease in their ability to produce foreign body granulomas against subcutaneously-implanted cotton pellets. Granulomas in stressed mice were smaller with a general inhibition of capsule formation and cellular infiltration as compared to control mice.

1. Jensen, M. M., Rasmussen, A. F., Jr., J. Immunol., 1963, v90, 21.

2. Rasmussen, A. F., Jr., Marsh, J. T., Brill, N. Q., Proc. Soc. Exp. Biol. and Med., 1957, v96, 183.

3. Yamada, A., Jensen, M. M., Rasmussen, A. F., Jr., ibid., 1964, v116, 677.

4. Chang, S. S., Rasmussen, A. F., Jr., Nature, 1965, v205, 623.

5. Christian, J. J., Williamson, H. O., Proc. Soc. Exp. Biol. and Med., 1958, v99, 385.

6. Meier, R., Schuler, W., Desaulles, P., Experientia, 1950, v6, 469.

7. Jensen, M. M., Rasmussen, A. F., Jr., J. Immunol., 1963, v90, 17.

8. Smith, L. W., Molomut, N., Gottfried, B., Proc. Soc. Exp. Biol. and Med., 1960, v103, 370.

9. Toivanen, P., Hulkko, S., Naatanen, E., Ann. Med. Exp. Fenn., 1960, v38, 343.

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The Potentiation of Pressor Responses to Tyramine by a Number of Amphetamine-Like Compounds. (31816)

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Eble and Rudzik(1) found that both amphetamine and reserpine enhance the acute pressor response to tyramine in the anesthetized dog. However, when amphetamine and reserpine were both given, in either order, the pressor response to tyramine was diminished (Eble and Rudzik(2)). Results of experiments designed to determine the structural requirements of compounds producing such a potentiation of tyramine and an antagonism of tyramine when these compounds are given in combination with reserpine are reported here.

Methods. Mongrel dogs weighing between 10 and 21 kg, unselected as to sex and anesthetized with sodium pentobarbital (32 mg/kg, i.v.), were used for these studies. Supplemental doses of 3.2 mg/kg were given as needed. Blood pressure from the carotid or femoral arteries was measured with a Statham transducer (Model P-23AC).

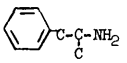
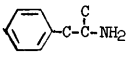
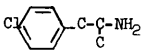
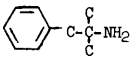
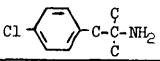
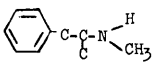
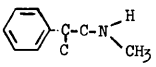
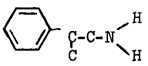
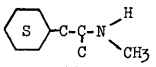
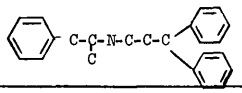
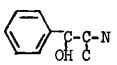
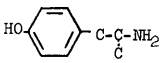
Drug injections were made *via* a polyethylene tube passed 3 to 5 cm into a femoral vein. The following compounds were used: tyramine hydrochloride, *d*-amphetamine sulfate, *l*-amphetamine sulfate, *p-cl*-amphetamine, phentermine hydrochloride, propylhexedrine, methamphetamine hydrochloride, prenylamine acetate, chlorphentermine hydrochloride, phenylpropylmethlamine, β-phenylpropyl amine, phenylpropanolamine, hydroxyamphetamine, and reserpine.

Results. The effects of a series of compounds, structurally related to amphetamine, on the pressor response to tyramine before and after reserpine are shown in Table I. The pressor response to tyramine was potentiated by all the compounds tested with the exception of prenylamine (Compound XI).

The administration of reserpine (1 mg/kg i.v.) after the test compound either potentiated the pressor response to tyramine further, antagonized it or had little or no effect on it. In our experiments the tyramine was administered 30-90 minutes after the reserpine, allowing for base blood pressure to return to pre-reserpine levels. Reserpine administered by itself markedly potentiated the pressor response to tyramine (Compound I). After either the *d*- or *l*-isomer of amphetamine (Compounds II and III) and reserpine the pressor response to tyramine was markedly reduced. Compounds substituted on the phenyl ring (Compound IV) or with an additional methyl group on the α-carbon (Compound V) also caused a decrease in the response to tyramine after reserpine. However,

when ring substitution and additional α-methyl substitution occurred in the same molecule (Compound VI) the response to tyramine after reserpine was increased. It appears that N-methylation of amphetamine (Compound VII) does not alter the activity of the compound. When the methyl group was placed on the β-carbon (Compound VIII) instead of the α-carbon, as in amphetamine, the response to tyramine after reserpine was markedly increased. N-methyl substitution on Compound VIII did not alter its activity

TABLE I

Compound No.*	Generic Name	Structure	Pressor Response to Tyramine mm Hg: Control	After Compound**	After Reserpine
I (5)	Reserpine	-	26 ± 4		63 ± 7 (< 0.001)
II (5)	d-Amphetamine		26 ± 3 (< 0.01)	61 ± 9	12 ± 1 (< 0.01)
III (5)	l-Amphetamine		26 ± 3 (< 0.01)	62 ± 6	25 ± 4 (< 0.01)
IV (5)	p-Cl-Amphetamine		33 ± 2 (< 0.001)	68 ± 5	42 ± 2 (< 0.02)
V (9)	Phentermine		24 ± 4 (< 0.001)	61 ± 6	34 ± 5 (< 0.05)
VI (6)	Chlorphentermine		25 ± 4 (< 0.01)	40 ± 5	56 ± 5 (< 0.02)
VII (5)	Methamphetamine		23 ± 2 (< 0.01)	48 ± 4	16 ± 3 (< 0.01)
IX (5)	Phenylpropylmethl-amine		22 ± 3 (< 0.05)	41 ± 4	80 ± 11 (< 0.05)
VIII (5)	Phenylpropylamine		22 ± 2 (< 0.001)	39 ± 1	79 ± 2 (< 0.001)
X (5)	Propylhexedrine		36 ± 6 (< 0.02)	57 ± 4	50 ± 7 (> 0.1)
XI (5)	Prenylamine		31 ± 8 (> 0.5)	34 ± 7	92 ± 10 (< 0.01)
XII (5)	Phenylpropanol-amine		26 ± 3 (< 0.02)	58 ± 5	57 ± 8 (> 0.5)
XIII (5)	Hydroxyamphetamine		27 ± 4 (< 0.05)	39 ± 4	53 ± 5 (< 0.02)

* No. of determinations ( ).

**All compounds given at a dose of 250 μg/kg i.v. with the exception of compound VI - 500 μg/kg i.v., compound IX - 500 μg/kg i.v. and compound XII - 1 mg/kg i.v.

(Compound IX).

Compound X, which had the phenyl ring saturated and the nitrogen methyl-substituted did not alter the response to tyramine after reserpine. When the size of the substitution on the nitrogen was increased to diphenylpropyl (Compound XI) the response to tyramine after reserpine was markedly increased.

The hydroxylation of the β-carbon of amphetamine (Compound XII) gave a compound which blocked the response to tyramine after reserpine, while the parahydroxylation of the phenyl ring of amphetamine (Compound XIII) resulted in a compound which in combination with reserpine, increased the response to tyramine.

Discussion. It has previously been shown that the pressor response to tyramine in the anesthetized dog was potentiated by either *d*-amphetamine or acute reserpine pretreatment (Eble and Rudzik(1)). When amphetamine and reserpine where given in combination, in either order, it was noted that the pressor response to tyramine was markedly decreased (Eble and Rudzik(2)). The potentiation of the pressor response to tyramine was observed with all the compounds tested, with the exception of prenylamine (Compound XI). It appears therefore that most compounds possessing a phenylisopropyl amine structure are capable of potentiating the pressor response to tyramine in the dog.

The response to tyramine after a combination of the test compounds and reserpine was varied and certain structural requirements could be established for this antagonism of the pressor response to tyramine. The blockade of the response to tyramine after reserpine is not stereo-specific since both the *d*- and *l*-isomers of amphetamine had the same effect. Nor did the N-methyl substitution alter the blocking activity.

The most marked alteration of blocking activity occurred when the compounds possessed a β-methyl instead of an α-methyl grouping (Compounds VIII and IX). When reserpine was administered following these compounds, the response to tyramine was either unaffected or further potentiated, *i.e.*, it would appear that only α-methyl substituted compounds are capable of blocking the pressor response to tyramine when combined with reserpine. Any substitution on the β-carbon appears to decrease the blocking activity. In the case of Compound X, where the subsequent administration of reserpine neither enhanced nor decreased the response to tyramine, it might be considered that the compound blocked the enhancement of tyramine by reserpine.

The potentiation of the pressor response to tyramine by either reserpine or amphetamine might be the result of a simple additive effect between agents which liberate amines. The blockade of the pressor response to tyramine by combinations of reserpine and certain amphetamine-like compounds would require a different explanation. This blockade may aid in studying further the mechanism of action of compounds which have both a direct and an indirect action on the blood pressure.

The finding that some compounds (V, VIII, XI, XIII and others) potentiate the pressor response to tyramine in the dog but do not subsequently antagonize tyramine in combination with reserpine suggests that these two phenomena are not related.

Summary. A series of compounds structurally similar to *d*-amphetamine were studied for their ability to potentiate the pressor response to tyramine and to antagonize it when given in combination with reserpine. All the compounds tested, with the exception of prenylamine, potentiated the pressor response to tyramine, but not all effected an antagonism to tyramine in combination with reserpine. This suggests that the two phenomena may not be related.

1. Eble, J. N., Rudzik, A. D., J. Pharm. Exp. Ther., 1965, v150, 375.

2. ———, ibid., 1966, v153, 62.

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