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Interaction between phenylpropanolamine and monoamine oxidase inhibitors

A. D'MELLO

The Department of Pharmacology and Therapeutics, The London Hospital Medical College, London, E.1, England

The role of monoamine oxidase in the potentiation of the pressor effect of phenylpropanolamine (norephedrine) by monoamine oxidase inhibitors has been investigated. *In vitro*, phenylpropanolamine was not a substrate of monoamine oxidase from guinea-pig liver. In spinal cats the pressor effects of both phenylpropanolamine and tyramine were potentiated by a monoamine oxidase inhibitor, nialamide, and by the microsomal enzyme inhibitor SKF 525-A, which is not a monoamine oxidase inhibitor. These results suggest that the enhanced pressor effect of phenylpropanolamine in the presence of monoamine oxidase inhibitors is caused by inhibition of other enzymes.

Pressor responses to indirectly acting sympathomimetic amines are greatly increased in the presence of monoamine oxidase inhibitors. An example in man is the potentiation of the pressor effect of phenylpropanolamine (norephedrine) by tranylcypromine (Cuthbert, Greenberg & Morley, 1969). This might occur as a result of an increase in the concentration of the amine at its site of action because its enzymatic metabolism by amine oxidase is inhibited. But phenylpropanolamine has a methyl group attached to the α-carbon atom of the aliphatic side chain, and it is known that some sympathomimetic amines of a similar structure (e.g. ephedrine, amphetamine) are not substrates of monoamine oxidase. Since it is uncertain if the enhanced pressor activity of phenylpropanolamine in the presence of a monoamine oxidase inhibitor is caused by inhibition of this or other enzymes, the interaction was investigated further.

EXPERIMENTAL

Manometry. Acetone dried guinea-pig liver powder as a source of amine oxidase was prepared according to Blaschko (1952). A suspension of the powder in M/15 phosphate buffer (pH 7·40) was incubated in oxygen at 37° in Warburg flasks in the presence of tyramine, phenylpropanolamine, or a mixture of the two amines. Their final concentrations were: liver powder in each flask 15 mg/ml, tyramine HCl 0·008M, phenylpropanolamine HCl 0·008M or 0·016M. The central well contained 0·3 ml 10% KOH to absorb CO_2. Endogenous substrate in the enzyme preparation was removed by washing with phosphate buffer before the final suspension was made. After equilibration, the uptake of oxygen by the enzyme during oxidative deamination was read for an hour at 10 min intervals.

Cat blood pressure. Cats, 1·5 to 2·0 kg, were anaesthetized with sodium pentobarbitone (50 mg/kg, i.p.) and then submitted to spinal section (Burn, 1952). The mean arterial b.p. was recorded from the carotid artery by a cannula and mercury manometer.

In one series of experiments duplicate control pressor responses to 100 and 250 μg of both tyramine and phenylpropanolamine were obtained by injecting the drugs into

the femoral vein at 15 min intervals. Such an interval avoided tachyphylaxis to the amines. After the control responses had been obtained, SKF 525-A (diethylaminoethyl diphenylpropyl acetate) (40 mg/kg) was infused intravenously for 1 h. Two h after the start of the infusion the injections of both amines were repeated in duplicate.

In another series of experiments cats were pretreated with nialamide, a monoamine oxidase inhibitor devoid of sympathomimetic activity (Ryall 1961), 50 mg/kg by intraperitoneal injection 20 h before the experiment. Pressor responses to 50 and 100 μg of both tyramine and phenylpropanolamine were obtained. These responses were compared with control responses from other untreated cats.

RESULTS

Manometry. Tyramine but not phenylpropanolamine was deaminated by the enzyme preparation and the second substance is therefore not a substrate of monoamine oxidase. However, when both amines were incubated with the enzyme simultaneously the rate of deamination of tyramine was decreased, perhaps because phenylpropanolamine competed with tyramine for attachment of the enzyme (Fig. 1).

Cat blood pressure. In each cat it was possible to obtain responses at two dose-levels for each amine before and after treatment with SKF 525-A (Table 1).

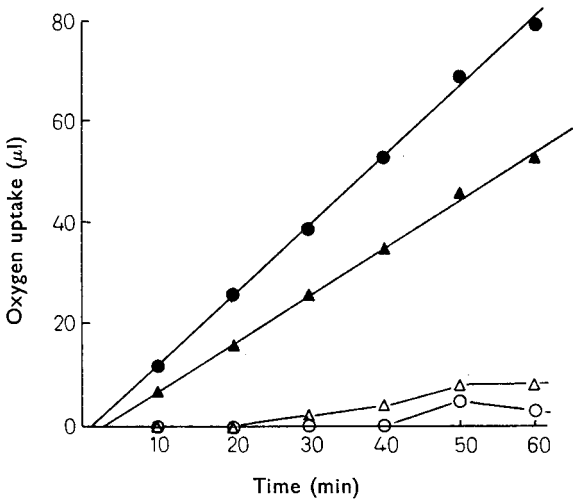

FIG. 1. Oxygen uptake (μl) by guinea-pig liver powder suspension with different substrates. Mean values of 4 experiments. ● Tyramine HCl 0·008M, ▲ Tyramine HCl 0·008M + phenylpropanolamine HCl 0·008M, △ Phenylpropanolamine HCl 0·008M, ○ Phenylpropanolamine HCl 0·016M.

Table 1. *Increases in mean arterial blood pressure (mm Hg) before and after SKF 525-A. Each value represents the mean of 2 determinations.*

	Tyramine				Phenylpropanolamine			
Cat	100 μg		250 μg		100 μg		250 μg	
No.	Control	SKF 525-A	Control	SKF 525-A	Control	SKF 525-A	Control	SKF 525-A
1	24	58	51	93	19	42	56	69
2	20	43	47	74	14	35	26	37
3	22	45	44	66	10	15	21	29
4	14	28	52	78	10	20	30	36
Mean	20·0	43·5	48·5	77·8	13·3	28·0	33·3	42·8

The difference in the pressor response of the two sympathomimetic amines was significant. There was a significant difference between the response to the low and high doses of each drug ($P < 0{\cdot}001$). The difference between the control pressor response and the response after treatment with SKF 525-A was significant ($P < 0{\cdot}001$). The estimates of the variance from the interactions "substrates x treatments" and "doses x treatments" were significantly different from the residual variance ($P < 0{\cdot}001$); therefore treatment with SKF 525-A significantly potentiated the effect of both tyramine and phenylpropanolamine at each dose-level.

Table 2. *Increases in mean arterial blood pressure* (mm Hg ± s.e.) *in untreated cats and in cats treated with nialamide*

		Untreated cats	After nialamide	Significance level
Tyramine	50 μg	3 ± 0·9	31 ± 2·1	$P < 0{\cdot}001$
	100 μg	22 ± 2·6	68 ± 3·2	$P < 0{\cdot}001$
Phenyl-propanolamine	50 μg	3 ± 0·6	34 ± 6·2	$P < 0{\cdot}01$
	100 μg	13 ± 1·9	81 ± 2·3	$P < 0{\cdot}001$

Tachyphylaxis to both sympathomimetic amines occurred to a varying degree after nialamide. In some cats it was not possible to obtain pressor responses to more than one dose of each sympathomimetic amine. Therefore it was impossible to use an experimental design similar to that devised for treatment with SKF 525-A where each cat received two different doses of each amine. In cats treated with nialamide there was considerable potentiation of the responses to both doses of each amine compared with the responses from untreated cats (Table 2).

DISCUSSION

Potentiation of the pressor effect of phenylpropanolamine by a monoamine oxidase inhibitor, tranylcypromine, has been observed in man by Cuthbert & others (1969). Phenylpropanolamine is a sympathomimetic amine with a methyl group attached to the α-carbon atom of the aliphatic side-chain. Such a structure usually precludes a substance from being a substrate of monoamine oxidases. *In vitro* experiments indicate that phenylpropanolamine is not a substrate of monoamine oxidase prepared from guinea-pig liver. Enhanced pressor activity to both phenylpropanolamine and tyramine was demonstrated in anaesthetized cats pretreated with nialamide, a monoamine oxidase inhibitor devoid of sympathomimetic activity (Ryall, 1961). However, SKF 525-A, a substance which inhibits liver microsomal enzymes (Brodie, 1956), but not monoamine oxidase (Dubnick, Morgan & Phillips, 1963), potentiated the pressor effect of both phenylpropanolamine and tyramine. These results show that phenylpropanolamine is not a substrate for monoamine oxidase and suggest that other enzymes are involved in its metabolism. The observation of Rand & Trinker (1968) that tyramine is metabolized by enzymes other than monoamine oxidase and that so called monoamine oxidase inhibitors are active against more than one type of enzyme system is confirmed. The interaction between phenylpropanolamine and monoamine oxidase inhibitors is thus probably due to inhibition of the binding or metabolism of the amine by these other enzymes.

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