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RESTORATION OF THE RESPONSE TO TYRAMINE BY METARAMINOL IN RESERPINIZED CATS

BY

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It is well known that depletion of the noradrenaline stores by treatment of animals with reserpine reduces or abolishes the response to tyramine. However, the response to tyramine may be restored by infusion of noradrenaline. This restoration is believed to be due to a partial refilling of the previously depleted stores with exogenous noradrenaline and a subsequent release by tyramine.

It has been shown that α-methylmetatyrosine is decarboxylated to form α-methylmetatyramine (Udenfriend & Zaltzman-Nirenberg, 1962). The metabolism proceeds further to form the active product metaraminol. This amine may enter the noradrenaline storage site and take over the function of neurochemical transmitter (Crout & Shore, 1964).

The present study was undertaken to determine whether or not metaraminol can restore the response to tyramine in reserpinized cats.

METHODS

Cats of either sex and of 2.0 to 3.5 kg body weight were used. After induction of anaesthesia with ether spinal preparations were made according to the method of Burn (1952). The movement of the nictitating membrane was recorded with an isotonic myograph; the weight on the nictitating membrane was 5 g. The blood pressure was recorded from a femoral artery with a pressure transducer (Linear-Core model P-1000).

Cats were administered 1.25 mg/kg of reserpine (Serpasil, Ciba) 24 hr before the experiments. Disulfiram (200 mg/kg) was administered intraperitoneally as a suspension 1 hr before the injection of α-methylmetatyramine or metaraminol.

The following substances were used: α-methylmetatyrosine, DL-α-methylmetatyramine, α-methylnoradrenaline hydrochloride, metaraminol bitartrate and tyramine hydrochloride. The details of dosage and routes of administration are given in Results.

RESULTS

Restoration of the response to tyramine by α-methylnoradrenaline or metaraminol. Infusions of either 1 mg of α-methylnoradrenaline or 0.5 mg of metaraminol during a 30-min period restored the action of tyramine on the blood pressure and on the nictitating membrane in the reserpinized cat (Figs. 1 and 2).

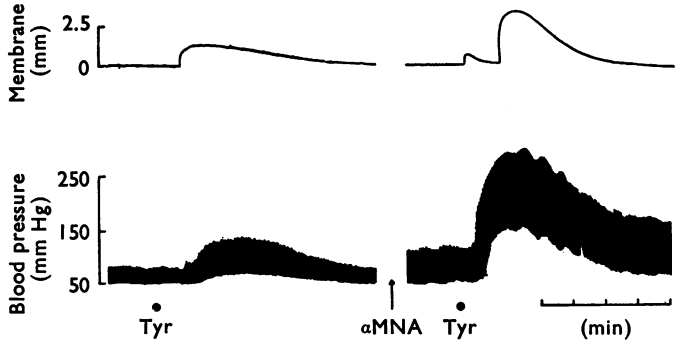

Fig. 1. Cat, 3 kg. Responses of the nictitating membrane and of the blood pressure to 1 mg/kg of tyramine (Tyr) 20 min before and 45 min after intravenous infusion of 1 mg of α-methyl-noradrenaline (αMNA) in a reserpinized spinal cat. This result is typical of three experiments.

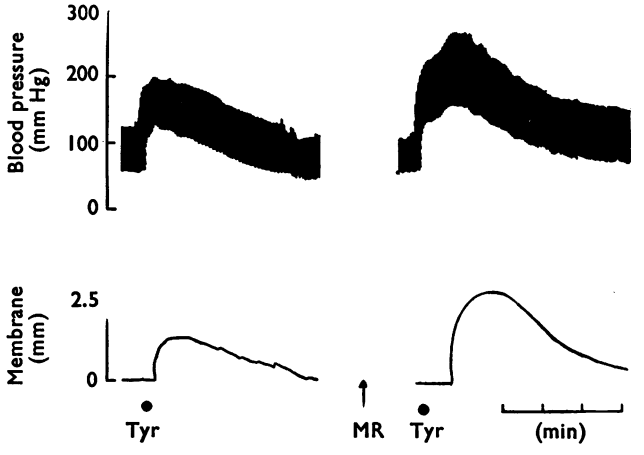

Fig. 2. Cat, 2.9 kg. Responses of the nictitating membrane and of the blood pressure to 1 mg/kg of tyramine (Tyr) 20 min before and 45 min after intravenous infusion of 0.5 mg of metaraminol (MR) in a reserpinized spinal cat. This result is typical of six experiments.

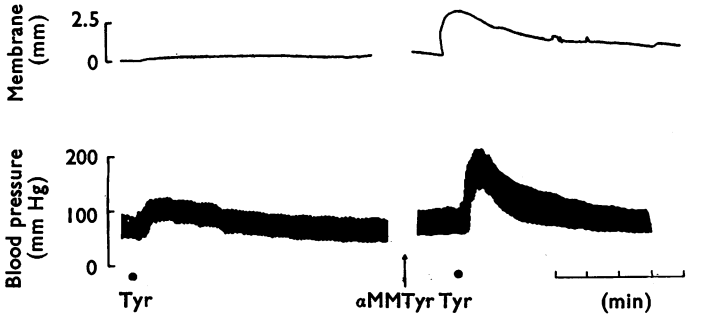

Fig. 3. Cat, 2.6 kg. Responses of the nictitating membrane and of the blood pressure to 1 mg/kg of tyramine (Tyr) 20 min before and 30 min after intraperitoneal injection of 2 mg of α-methyl-metatyramine (αMMTyr) in a reserpinized spinal cat. This result is typical of four experiments.

Restoration of the response to tyramine by α-methylmetatyrosine and α-methylmetatyramine. Administration of 2 mg of α-methylmetatyramine restored the response of the nictitating membrane and of the blood pressure to tyramine (Fig. 3). Like α-methylmetatyramine, α-methylmetatyrosine successfully restored the response of the blood pressure and of the nictitating membrane to tyramine. The peak restoration of the tyramine action occurred at 3 hr after α-methylmetatyrosine had been injected, since after that period there was no further increase in response (Fig. 4).

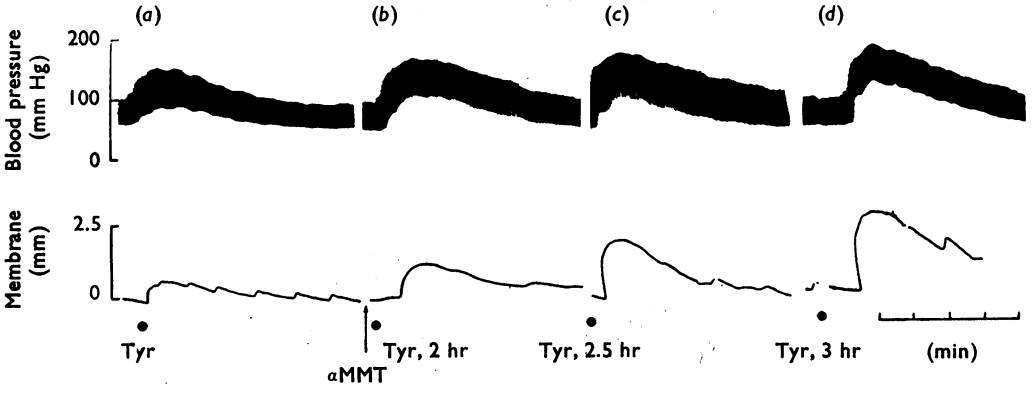

Fig. 4. Cat, 2.5 kg. Responses of the nictitating membrane and of the blood pressure to 1 mg/kg of tyramine (Tyr); (*a*) 20 min before; (*b*) 2 hr after; (*c*) 2.5 hr after; and (*d*) 3 hr after intraperitoneal injection of 10 mg of α-methylmetatyrosine (αMMT) in a reserpinized spinal cat. This result is typical of four experiments.

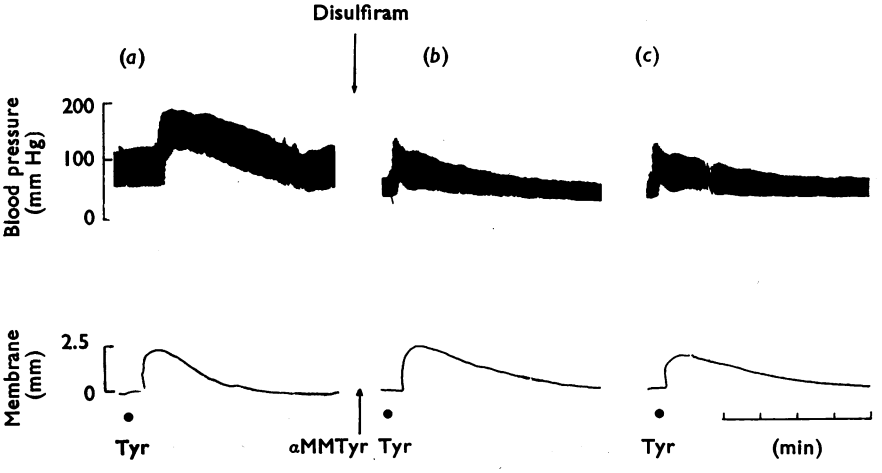

Fig. 5. Cat, 2.6 kg. Effect of disulfiram on the restoration by α-methylmetatyramine of the response to tyramine of the nictitating membrane and of the blood pressure in a reserpinized spinal cat. Disulfiram (200 mg/kg) was given intraperitoneally 60 min before intraperitoneal administration of 2 mg of α-methylmetatyramine (αMMTyr). Responses to 1 mg/kg of tyramine (Tyr): (*a*) 20 min before disulfiram; (*b*) 30 min after α-methylmetatyramine; and (*c*) 60 min after α-methylmetatyramine. This result is typical of four experiments.

Effect of disulfiram on the restoration of the action of tyramine by α-methylmetatyramine. Treatment of animals with disulfiram before the administration of α-methylmetatyramine inhibited the restoration of the response of the nictitating membrane and of the blood pressure to tyramine by α-methylmetatyramine (Fig. 5). In fact the response to tyramine was slightly decreased as compared with controls. The capacity of 0.5 mg of metaraminol to restore the vasopressor response and the response of the nictitating membrane to tyramine in the reserpinized cat was not impaired by disulfiram.

DISCUSSION

Burn & Rand (1958) reported that depletion of noradrenaline stores by reserpine greatly reduced the response to tyramine of the nictitating membrane and of the blood pressure; the responses to tyramine were partly restored after an infusion of noradrenaline. They interpreted this phenomenon as a refilling by exogenous noradrenaline of the previously depleted stores and as a release by tyramine of the stored noradrenaline. Similar restoration of the effects of tyramine were obtained when α-methyldopa was used (Day & Rand, 1964), possibly because of conversion to α-methylnoradrenaline. In the present study we have shown that low doses of metaraminol could also restore the response to tyramine.

Restoration of the response to tyramine is not restricted to metaraminol, since its precursors α-methylmetatyrosine and α-methylmetatyramine could also restore the response to tyramine. The restored response after α-methylmetatyramine could be due to a release of retained α-methylmetatyramine itself or of metaraminol synthesized by hydroxylation of this amine. The restored response after α-methylmetatyrosine is in all likelihood due to release of either α-methylmetatyramine or metaraminol or both, synthesized from this substance *in vivo* and then retained. This amino-acid is not a pressor agent, nor does it produce other sympathomimetic actions, even when administered in doses which yield large amounts of the amines.

When disulfiram was used to inhibit dopamine-β-oxidase, α-methylmetatyramine failed to restore the actions of tyramine in reserpinized animals. Disulfiram did not interfere with the restoration by metaraminol of the actions of tyramine in reserpinized animals. These findings indicate that β-hydroxylation is required for the restoration of the actions of tyramine by α-methylmetatyramine and provide further evidence for the view that only the β-hydroxylated product of α-methylmetatyramine is the active amine.

The finding that metaraminol could restore the response to tyramine is interpreted as meaning that it too can be retained in storage sites critical for tyramine response and subsequently be released by tyramine. Consistent with this are the findings of Crout, Alpers, Tatum & Shore (1964), who have recently reported that sympathetic nerve stimulation can release metaraminol from the hearts of the animals previously treated with metaraminol. Their study and this one provide pharmacological evidence that metaraminol is bound in the nerve endings at sites ordinarily occupied by noradrenaline.

SUMMARY

1. In the reserpinized spinal cat the responses of the nictitating membrane and of the blood pressure to tyramine were restored by infusion of α-methylnoradrenaline and a low dose of metaraminol.

2. α-Methylmetatyrosine and α-methylmetatyramine were also successful in restoring the response to tyramine.

3. Inhibition of dopamine-β-oxidase with disulfiram antagonized the restoration by α-methylmetatyramine but not by metaraminol.

4. It is concluded that metaraminol occupies the same place as is occupied by noradrenaline and that only the β-hydroxylated derivative of α-methylmetatyramine and α-methylmetatyrosine is capable of restoring the response to tyramine.

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REFERENCES

BURN, J. H. (1952). *Practical Pharmacology*. Oxford: Blackwell.

BURN, J. H. & RAND, M. J. (1958). The action of sympathomimetic amines in animals treated with reserpine. *J. Physiol. (Lond.)*, **144**, 314–336.

CROUT, J. R., ALPERS, H. S., TATUM, E. L. & SHORE, P. A. (1964). Release of metaraminol (aramine) from the heart by sympathetic nerve stimulation. *Science*, **145**, 828–829.

CROUT, J. R. & SHORE, P. A. (1964). Release of metaraminol (aramine) from the heart by sympathetic nerve stimulation. *Clin. Res.*, **12**, 180.

DAY, M. D. & RAND, M. J. (1964). Some observations on the pharmacology of α-methyldopa. *Brit. J. Pharmacol.*, **22**, 72–86.

UDENFRIEND, S. & ZALTZMAN-NIRENBERG, P. (1962). On the mechanism of the norepinephrine release produced by α-methyl-meta-tyrosine. *J. Pharmacol. exp. Ther.*, **138**, 194–199.