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Interaction between tyramine and iproniazid on guinea-pig atria

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Summary

The inhibition of monoamine oxidase (MAO) by iproniazid may be antagonized by large doses of tyramine as shown by the restoration, or otherwise, of inotropic responses to tyramine in isolated atria from guinea-pigs that had been treated with reserpine.

Introduction

No positive inotropic response to tyramine is obtained in isolated atria from reserpine-treated guinea-pig but after treatment with iproniazid and incubation with noradrenaline the response to tyramine reappears (Furchgott, 1964; Furchgott & Sanchez Garcia, 1968). Although iproniazid is considered to be an irreversible inhibitor of monoamine oxidase (MAO), previous studies (Garcia de Jalón, Serrano & Lastra, 1971; Garcia Garcia, Velasco Martin, Martinez-Sierra & Sanchez Garcia, 1972) have led us to think that this action of iproniazid might be antagonized by tyramine because of competition for a common transfer site at the neuronal membrane or by competition with the inhibitor for the active site of the enzyme. If this is so, the recovery of the response to tyramine, in reserpinized guinea-pig isolated atria, pretreated with iproniazid and noradrenaline, should be prevented if equilibration with iproniazid is carried out in the presence of an excess of tyramine.

Methods

Left atria from guinea-pigs, weighing from 500 to 800 g and given reserpine (5 mg/kg), 18 to 24 h beforehand, were prepared and mounted as previously described by Furchgott, Kirpekar, Rieker & Schwab (1963). Each half atrium served as a control. The atria were suspended in Krebs bicarbonate solution aerated with 95% O_2 and 5% CO_2 and containing 10 mM glucose and 10 μg/ml of the disodium salt of ethylene diamine tetraacetic acid. Atria were attached to a force-displacement transducer (Grass, model FTO3, connected to a Grass polygraph, model 7 PCP-D) with an initial tension of 1 g and driven by two Grass stimulators (S D-5 and S-4) at a frequency of 0·5 Hz and 5 ms duration. Voltage was set at 20% above threshold.

The drugs used were: (−)-noradrenaline bitartrate (Nutritional Biochem. Corp.); tyramine hydrochloride (Nutritional Biochem. Corp.); iproniazid phosphate (Roche); reserpine (Ciba). The doses are expressed in terms of g/ml of the bath solution.

Results

In the control preparation (A and A^1, Fig. 1), one of a series of 15 experiments, serial exposure of the atrium (from a reserpine-treated guinea-pig) to iproniazid and noradrenaline led to a return of a positive inotropic response to tyramine. However, as shown by B and B^1 (Fig. 1), simultaneous exposure of the atrium to tyramine and iproniazid prevented the subsequent stimulating effect of tyramine as was seen in the control preparation after incubation with noradrenaline. In another series of 15 experiments, treatment with tyramine after washout of the iproniazid but before incubation with noradrenaline was found to produce a similar block of the post-noradrenaline tyramine responses. Finally, in 10 experiments, atria exposed to a large dose (500 μg/ml) of iproniazid 20 min after washing out the noradrenaline still responded to tyramine (1 μg/ml), in the usual way 5 min later.

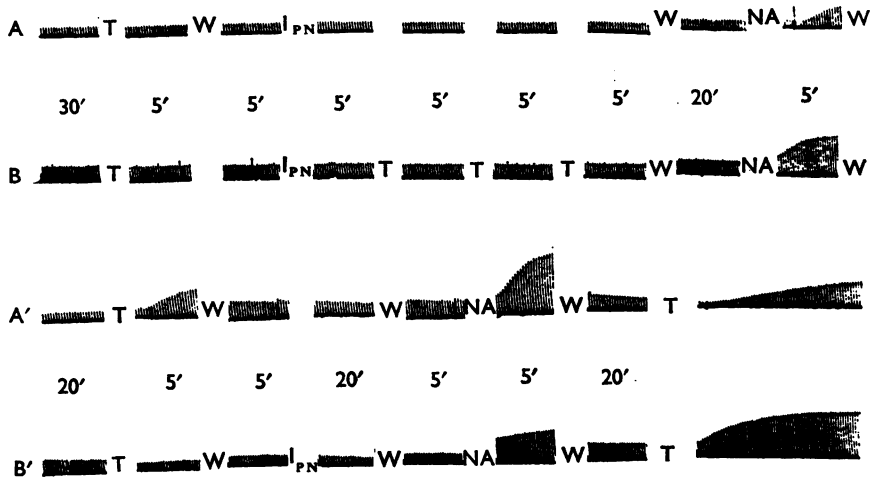

FIG. 1. Isometric contractions from stimulated left atrial preparations obtained from a reserpine-treated guinea-pig. A and A^1: records from control half of atrium, B and B^1: records from treated half of atrium, T: tyramine, 100 μg/ml, IPN: iproniazid, 100 μg/ml, NA: noradrenaline, 1 μg/ml. After 30 min rest, tyramine was added to each preparation to test for the absence of inotropic effects. After 5 min, the control preparation (A) was washed and then iproniazid was added to the preparations and left for 20 minutes. Tyramine is a good substrate for MAO and the bath concentration of tyramine was kept high by adding more at 5 min intervals. After equilibration with iproniazid both preparations were thoroughly washed and after another 20 min period they were incubated first with noradrenaline for 5 min and then, after more washing, with tyramine for 5 minutes. A positive inotropic response to tyramine appeared only in the control preparation. After washing out the tyramine from both preparations, the response to tyramine in the treated (B^1) preparation was restored after giving it the same combination of exposure to iproniazid and noradrenaline as was given to the control preparation.

Discussion

The administration of tyramine to guinea-pig isolated atria produces a positive inotropic response due to catecholamine release. Tyramine has no effect on atria from reserpine-treated guinea-pigs because the neuronal catecholamine pool is depleted; if MAO is inhibited by iproniazid and the atria are then incubated with noradrenaline, the positive inotropic response to a subsequent dose of tyramine reappears. However, as shown in this paper, when iproniazid is given in the presence of a high concentration of tyramine followed by incubation with noradrenaline, then no response is obtained to a subsequent dose of tyramine (Figure 1).

These results can be explained by assuming that the large dose of tyramine blocked the inhibitory effect of MAO produced by iproniazid. This blocking effect might be explained in several ways:

1. Tyramine might react chemically with the iproniazid ; this possibility is unlikely because of the finding that a large dose of iproniazid did not block the release of noradrenaline by a small dose of tyramine.
2. The fact that iproniazid failed to block the incorporation of tyramine into the sympathetic endings suggests that the transfer site at the neuronal membrane for tyramine is different from the one for iproniazid ; however this does not exclude the possibility that large doses of tyramine might block the uptake of iproniazid through its transfer site.
3. The experiments in which tyramine was given after MAO inhibition by iproniazid and where no positive inotropic response to tyramine was obtained after incubation with noradrenaline support the possibility that tyramine can displace iproniazid from its complex with MAO thus reactivating the enzyme.
4. Finally, because tyramine has a common transfer site with noradrenaline (Commarato, Brody & McNeill, 1969), it is possible that the washing was not sufficient to eliminate tyramine from the adrenergic endings (due to the large doses administered) leading to blockade of the uptake and/or retention of noradrenaline ; however, this is an unlikely explanation because in the second series of experiments neither several washes nor a new incubation with noradrenaline was able to restore the positive inotropic response to tyramine.

Recently (Furchgott, Sanchez Garcia, Wakade & Cervoni, 1971) it has been shown that the inhibition of MAO by bretylium could be blocked by previous treatment with tyramine but not the inhibition produced by iproniazid or pheniprazine. This discrepancy with our results is probably explained by the different doses of tyramine administered. These authors used doses of tyramine about 20 times lower than the dose used by us and doses of iproniazid were approximately 5 times higher than ours. These results are in agreement with our previous results (unpublished data), in which tyramine in doses of 1 μg/ml and 10 μg/ml were not sufficient to annul the inhibitory effect of MAO by iproniazid (100 μg/ml).

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