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The rôle of octopamine in tachyphylaxis to tyramine

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BURN AND RAND[1] suggested that the sympathomimetic action of tyramine is a consequence of release of norepinephrine from tissue stores. Direct evidence to support this hypothesis has been forthcoming from a number of laboratories. When repeated doses of tyramine are administered tachyphylaxis develops. With each successive dose of tyramine there is diminished release of norepinephrine.[2] Tachyphylaxis, however, develops before the norepinephrine stores are completely depleted. It has been demonstrated recently that tyramine is taken into sympathetic nerves and converted by β-hydroxylation to octopamine.[3, 4] Octopamine is retained in part by the "microsomal" fraction, which contains the norepinephrine storage granules.[5] It can be released by nerve stimulation[6, 7] and by drugs that deplete norepinephrine.[7] We have examined the octopamine content of the heart during the development of tachyphylaxis to tyramine.

Tyramine-^{3}H (G.L.), obtained from New England Nuclear Corp., Boston, Mass., was diluted with unlabeled tyramine to a specific activity of 5 μc/μmole. Enzymatic conversion of this tyramine-^{3}H to octopamine-^{3}H did not result in production of significant amounts of tritiated water (unpublished observations). Male Sprague-Dawley rats weighing 200 to 250 g received one, two, or three doses of the labeled amine (10 mg/kg, i.m.) at 15-min intervals. One group of rats which had received three injections of the labeled amine was given a fourth dose of unlabeled tyramine (10 mg/kg). Another group received three doses of unlabled tyramine (10 mg/kg) and a fourth dose of labeled tyramine (10 mg/kg). The animals were killed by a blow on the head 15 min after the last dose of tyramine. The hearts were removed, homogenized in ice-cold 0·4 N perchloric acid, and the supernatant analyzed for norepinephrine[8] and tritiated octopamine.[5]

The results (Fig. 1) indicate that part of the administered tyramine was converted to octopamine. The extent of conversion paralleled the norepinephrine depletion so that the total β-hydroxylated amine content of the heart was increased only slightly. The third and fourth doses of tyramine did not appear to release significant quantities of norepinephrine confirming the observations of Potter *et al.*[2] Octopamine-^{3}H in the heart was largely depleted after administration of the fourth dose of unlabeled tyramine. When three doses of unlabeled tyramine had been given, the amount of octopamine-^{3}H found in the heart after administration of tyramine-^{3}H corresponded to the amount of octopamine-^{3}H depleted by unlabeled tyramine. Thus, the fourth dose of tyramine released mainly octopamine, in an amount equivalent to the norepinephrine released by the first two doses of tyramine.

Although large amounts of tyramine (19–28 mμmole/heart) remained in the tissue, this amine may have been present largely in the myocardial cells. Octopamine accumulation, however, is dependent upon sympathetic innervation,[3, 4] and it is likely that this amine is confined to the sympathetic nerve tissue in the heart.

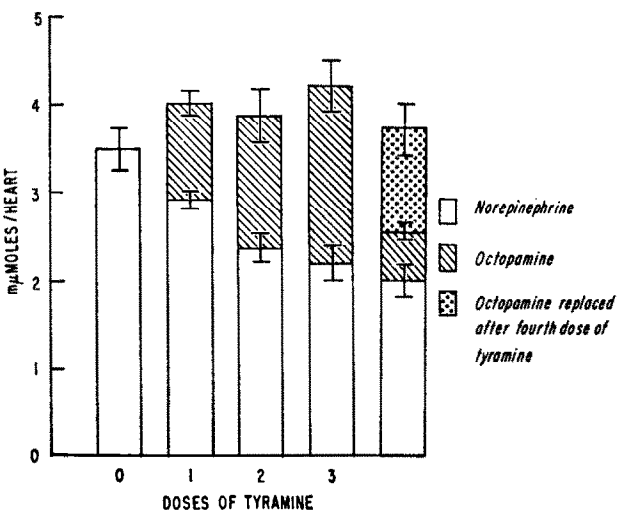

FIG. 1. Norepinephrine and octopamine-^{3}H content of the hearts of rats which receive 0, 1, 2, 3, or 4 doses of tyramine-^{3}H as described. The fifth column indicates residual norepinephrine and octopamine-^{3}H present after three doses of tyramine-^{3}H and a fourth dose of unlabeled tyramine (striped area), as well as the octopamine-^{3}H formed from tyramine-^{3}H administered after three doses of unlabeled tyramine (stippled area). There was no significant difference in the heart weights (630 ± 30 mg) of the various groups, so that the results are expressed as the mean amine content (mμmole/heart) ± S.E.M. for groups of six animals.

These results suggest that octopamine formed in the heart during administration of repeated doses of tyramine may replace the relased norepinephrine. Further doses of tyramine release the same number of β-hydroxylated amine molecules, but it is the octopamine that replaces norepinephrine rather than the residual norepinephrine which is largely released. Blaschko[9] suggested that tyramine tachyphylaxis may be a consequence of binding of the amine at the site of norepinephrine storage. It appears, however, that the β-hydroxylated derivative of tyramine rather than the amine itself replaces the catecholamine.

It appears that, after several doses of tyramine, octopamine formed from the administered amine replaces norepinephrine and protects the residual norepinephrine from further release by substituting for the catecholamine at the binding sites from which tyramine releases the neurotransmitter. This may explain why only partial (60%) depletion of norepinephrine stores by tyramine results in reduced responses to the amine, while only a small fraction (less than 20%) of the norepinephrine store is required for the action of tyramine when catecholamine stores are largely depleted by reserpine administration.[10] The depletion induced by reserpine does not appear to involve replacement of the

catecholamine by another amine molecule, and tyramine can still release sufficient amounts of norepinephrine to evoke a response.

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