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Received July 20, 1962. P.S.E.B.M., 1963, v112.

Circulatory Responses to Cardioaccelerator Nerve Stimulation after Induction of Tyramine Tachyphylaxis. (27943)

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It is now clear that norepinephrine (NE) can be released from sympathetic nerve endings not only by nerve stimulation, but also by a number of aromatic amines, including tyramine(1). It has recently been shown that after a prolonged infusion of tyramine, the physiologic response to subsequent injection of this amine is virtually abolished, in spite of the finding that substantial quantities of NE remain in the tissues(2). If the physiologic response to neural stimulation could be shown to remain unimpaired despite loss of responsiveness to tyramine, this would suggest that the NE released by these two stimuli is not derived from a homogeneous pool.

Methods. The chronotropic and inotropic responses to stimulation of the cardioaccelerator nerve were compared before and after an infusion of tyramine. Six dogs weighing 10.2 to 12.8 kg were lightly anesthetized with a chloralose-urethane mixture given intravenously and, following a right thoracotomy, right ventricular contractile force was determined with a Walton-Brodie strain gauge arch. Supramaximal stimulation of the right cardioaccelerator nerve at a frequency 10/second was carried out with a Grass stimulator. Tyramine was injected intravenously at a dose of 60 μg/kg before and 1000 μg/kg after a one-hour infusion of 200 μg/kg/min of this substance.

Results. Prior to the tyramine infusion cardioaccelerator nerve stimulation produced an average increase in heart rate of 75 $\pm$ 11 beats/min and of right ventricular contractile force of 58% $\pm$ 25%. Administration of 60 μg/kg tyramine at this time resulted in an average increase in heart rate of 61 $\pm$ 8 beats/min and of contractile force of 108% $\pm$ 19%. Immediately following the one-hour infusion of tyramine, the response to stimulation of the cardioaccelerator nerve was essentially unchanged, with an average increase in heart rate of 67 $\pm$ 10 beats/min and in contractile force of 54% $\pm$ 26%. At this time, 1000 μg/kg of tyramine produced an average increase in heart rate of only 13 $\pm$ 4 beats/min and in contractile force of 13% $\pm$ 9% (Fig. 1).

Discussion. A number of investigators have suggested that the NE pool at the sympathetic nerve endings is not a homogeneous one. Trendelenburg has proposed a distinction between NE which is "available" for release by tyramine and nerve stimulation and "bound" NE(3). In support of this hypothesis of 2 compartments of NE stores in the tissues, it has recently been shown that following depletion of myocardial NE stores by reserpine, the physiologic response to tyramine is dependent upon the presence of only a small fraction of the normal tissue NE concentration(4,5). In addition, Potter and associates have demonstrated that isotopically labelled NE remaining in the heart for long periods of time is mainly confined to a tightly bound store and unavailable for release by tyramine, which also suggests the presence of more than one tissue store of NE(6).

It was shown previously that an infusion of 200 μg/kg/min of tyramine for one hour reduced atrial NE content by an average value of 43% of the control, and abolished the cardiovascular responses to further injec-

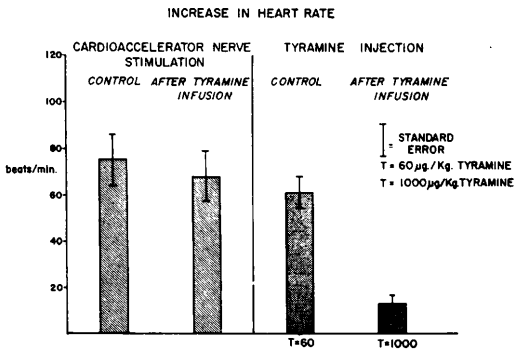

FIG. 1. Average increase in heart rate produced by stimulation of right cardioaccelerator nerve before and after infusion of 200 µg/kg/min of tyramine for 1 hr is shown on the left side of this figure. On the right half, average increases in heart rate produced by 60 µg/kg tyramine in control period and 1000 µg/kg tyramine after tyramine infusion are shown.

tions of this amine almost completely (2). In the present study it was also shown that the physiologic response to tyramine was essentially abolished after a similar infusion. However, there was no significant reduction in chronotropic and inotropic responses to cardioaccelerator nerve stimulation. In a recent study of the mechanism of development of tachyphylaxis to phenylalkylamines, it was suggested that the response of the nictitating membrane to nerve stimulation was unaffected after the development of amphetamine tachyphylaxis(7). Since, in the studies reported herein, nerve stimulation was evidently capable of releasing NE, when the store of NE available to release by tyramine was depleted, it is clear that some of the "available" NE can be released by nerve stimulation but not by tyramine. Thus, in addition to the concept that the NE in sympathetic nerve endings may exist in "bound" and "available" compartments, it must be considered that the NE available for release is further subdivided functionally. This subdivision may result either from heterogeneity of the readily releasable NE, or conceivably from the saturation of an intermediate step in the release of NE by tyramine.

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Received July 27, 1962. P.S.E.B.M., 1963, v112.

Desulfuration of Thiourea by Saliva.* (27944)

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The enzymatic desulfuration of thiourea by a cytoplasmic particulate system prepared from sheep thyroid has been described by Maloof and Spector(1). A known association exists between phenylthiocarbamide (PTC) non-tasting, and pathologic thyroid states(2-5). It has also been shown that persons who are relative non-tasters for PTC are relative non-tasters of thiourea and other thioamides such as D,L-goitrin and propylthiouracil(4,6). Because of these findings it was hypothesized that a thioamide desulfurating enzyme might be the common bio-

* This work was supported in part by research grants from Nat. Inst. Health and from the Nat. Science Foundation.

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