PHARMACOLOGICAL REVIEWS
Vol. 18, No. 1, Part I

Printed in U.S.A.

SECTION IV

Properties of Adrenergic Tissues

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A. INTRODUCTORY REMARKS

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During the 10 years which have passed since the subcellular particles containing norepinephrine (NE) were first demonstrated in nerves or organs (2) it has become increasingly evident that they play a fundamental role in the adrenergic transmission process. By various homogenization and centrifugation techniques the granules can be obtained in a relatively pure form allowing detailed studies of their properties *in vivo* and *in vitro*.

On incubation, the isolated particles from bovine splenic nerves give off their NE at a characteristic rate (3). Using tritiated NE, Potter and Axelrod (14) found essentially the same release rate also for granules from the rat's heart, later confirmed for rabbit's heart with unlabeled NE (5). This release rate differs considerably from that of adrenal medullary granules as described by Hillarp and Nilson (9). Thus the half-time for bovine nerve granules is about 10 min at pH 7.5 while that of adrenal medullary granules is more than 10 times longer. The difference indicates important differences in their properties (cf. 15) (fig. 1).

Large amounts of an adrenaline-like substance have earlier been observed in the vesicular gland of the bull (1); this later proved to be NE. In a recent study of subcellular granules from this organ (8) it was found that the NE release rate at 37°C and pH 7.5 was on an average 33 min, or about 3 times that of the splenic nerve granules. The effect of reserpine 10^{-5} M in the incubation medium was a slight inhibition of the release rate compared to the strong inhibition on splenic nerve granules (4). Also with regard to the actions of other drugs, such as prenylamine (Segontin) and phenoxybenzamine, the inhibitory action on the NE release from bull vesicular gland granules was much weaker than that found with splenic nerve granules. With the histochemical fluorescence technique of Falck and Hillarp the catecholamine-containing structures in the tissue were shown to consist entirely of nerves (13).

These observations show that the subcellular NE-containing particles may vary greatly in their properties in different adrenergic structures even if the histochemical appearance of these may be similar.

The different kinds of catecholamine granules thus seem to possess inherent mechanisms for determining a characteristic release rate. It is tempting to assume that such a mechanism is highly significant as a rate-limiting factor, permitting the nerve granules to discharge NE at a high rate while preventing excessive amine release from other sources, rich in NE, such as the adrenal medulla.

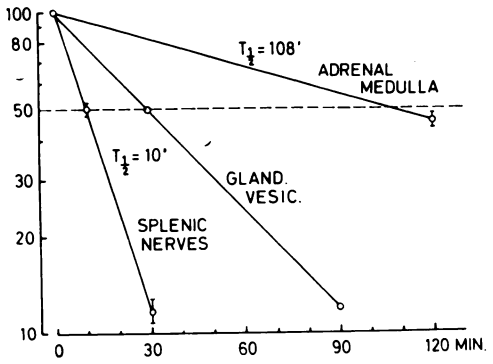

FIG. 1. Isolated granules from bovine tissues (splenic nerves, vesicular gland of bull, adrenal medulla) incubated in isotonic K-phosphate buffer 37°C, pH 7.5. Ordinates: NE content in sedimented granules after incubation, in percent of original amount (for adrenal medullary granules E + NE).

The rapid uptake of NE, injected *in vivo*, in the particulate fraction of the rabbit heart after depletion with prenylamine (10), or decaborane (6), in connection with the constant fraction of granule-bound NE, indicates a rapid equilibrium of the NE content between the extragranular and the granular storage sites, as observed also by Stjärne (15) and Michaelson *et al.* (11). Similarly the rapid refilling of the prenylamine-depleted rabbit heart with NE, following injection of octopamine or tyramine and, to a lesser extent, phenylethylamine, points to a rapid uptake of the first-mentioned amines (7) at granular sites. The significance of the binding groups of the amine molecule has recently been discussed by Musacchio *et al.* (12).

The important role of the NE granules for the physiologic function of the adrenergic nerve structures is further indicated by the recent finding that isolated splenic nerve particles are able to synthesize NE from dopa (16) (*cf.* Stjärne, Section IV F). From these and other recent findings it appears that the nerve granules play a determining role in the synthesis, storage and time course of release of NE. These processes may be strongly acted upon by a variety of drugs, which thereby can influence adrenergic nerve transmission.

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