Chapter 6

Synthesis, Uptake and Storage of Catecholamines in Adrenergic Nerves, The Effect of Drugs

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With 9 Figures

A. Introduction

The finding that the sympathomimetic agents in chromaffin cells and in adrenergic nerves are stored in apparently similar subcellular particles has sometimes led to the belief that the mechanisms for uptake, storage and release of the active compounds are identical or at least very similar. Detailed studies, mainly on isolated particles, have shown, however, that although similarities occur, important differences between the properties of the chromaffin cell particles and those in the adrenergic nerves exist. Thus nerve particles after partial depletion readily take up amines from a suspension medium to the original content or even higher in the presence of ATP-Mg++, whereas chromaffin cell particles containing either adrenaline or noradrenaline lack this property. Some drugs like phenoxybenzamine inhibit the release of noradrenaline from nerve particles but enhance the release from adrenal medullary granules. Striking differences in osmotic behaviour between chromaffin cell particles and nerve particles have also been described.

Moreover, there is increasing evidence that not all adrenergic nerve particles are of the same kind. Those appearing in the short adrenergic neurons in the male accessory reproductive organs show a different behaviour from those present in the ordinary adrenergic neurons, e.g. in the spleen. It is possible that the adrenergic nerve particles in the CNS have special properties, although little is known in this respect.

The important question of the mechanism of amine release from the chromaffin cells and adrenergic nerve terminals is still under debate and will not be discussed in this Chapter; it is only mentioned here since certain data indicate that the release mechanisms may differ, not only as regards the spontaneous release rate in vitro, but also more fundamentally, with respect to the nature of the releasing process in vivo.

B. Adrenergic Nerves

I. Synthesis

1. Main Synthetic Pathway

Synthesis of adrenaline occurs in vivo from phenylalanine and tyrosine (Gurin and Delluvia, 1947; Udenfriend et al., 1953) and from dopa and dopamine (Udenfriend and Wyngaarden, 1956). The formation of noradrenaline as a step in the synthetic pathway was originally suggested by Blaschko (1939) and by

H. Blaschko et al., Catecholamines
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HOLTZ (1939) following the discovery of dopa decarboxylase by HOLTZ et al. (1938). This was confirmed in vitro by GOODALL and KIRSHNER (1957) who showed that tyrosine is converted in a sequence to dopa, dopamine, noradrenaline and adrenaline by enzymes in the adrenal medulla. This pathway could later be confirmed also for adrenergic nerves (GOODALL and KIRSHNER, 1958) and for organs containing adrenergic nerves (SPECTOR et al., 1963a).

In the first step tyrosine serves as substrate for the enzyme tyrosine hydroxylase which is present in the axoplasm (NAGATSU et al., 1964). The DOPA formed is transformed to dopamine by L-DOPA decarboxylase which also occurs in the axoplasm. Dopamine is subsequently oxidized to noradrenaline with the aid of the enzyme dopamine-β-hydroxylase which is present in the storage particles (Fig. 1).

![Chemical structures](https://example.com/chemical Structures.png)

**Fig. 1.** Biosynthetic pathway for noradrenaline

### a) Tyrosine Hydroxylase

Since the formation of tyrosine from phenylalanine occurs in a variety of tissues outside the adrenergic neuron it seems appropriate to regard the formation of DOPA from tyrosine as the first synthetic step in this context. Tyrosine, which is generally available in the body fluids, can enter the adrenergic axon, where tyrosine hydroxylase is present. Whether or not special "pump" or "carrier" mechanisms are required for the entrance of tyrosine into the axon is not known, but it has been assumed that this process is facilitated by a "permease".

While tyrosine generally is a poor substrate for amino acid decarboxylases it is transformed into an efficient substrate by hydroxylation in the 3-position of the ring. The active enzyme was isolated and characterized by NAGATSU et al. (1964) (cf. UDENFRIEND, 1966). It is present in tissues which normally contain noradrenaline or adrenaline. The enzyme requires tetrahydropyridines, e.g. tetrahydrofolic acid, and is activated by divalent iron (IKEDA et al., 1965). Tyrosine hydroxylase catalyzes the oxidation of phenylalanine to tyrosine as well as the following step from tyrosine to DOPA.

The hydroxylation of tyrosine to DOPA is slower than the subsequent decarboxylation and β-hydroxylation and therefore rate limiting (SPECTOR et al., 1963a; LEVITT et al., 1965). The activity of the enzyme is inhibited by phenylalanine as well as by DOPA and noradrenaline, which may well constitute a feedback control mechanism, regulating the synthesis rate (NAGATSU et al., 1964).

### b) DOPA-Decarboxylase

The second step in the biosynthesis of the adrenergic neurotransmitter, the formation of dopamine from L-DOPA, is catalyzed by an efficient enzyme, L-DOPA decarboxylase, discovered in the mammalian kidney by HOLTZ et al.