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Cellular Control of the Uptake, Storage and Release of Catecholamines

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In experimental studies on sympathetic nerves it is easier to analyse separately the ability of this tissue to store, release and take up noradrenaline than it is to study the activity of the whole neuron. However, we want to know how these different properties are integrated in such a way that they complement each other. For example, why does the nerve not only release noradrenaline but also take it up? Since the nerve can rapidly synthesize noradrenaline, why does it have to store it? That we can now begin to answer these, and related, questions is due not to the application of any one experimental approach but rather to the use of several, chiefly those of the morphologist, biochemist and pharmacologist.

The current state of our knowledge about the uptake, storage and release of noradrenaline will show how these properties of the neuron are organized and controlled such that the cell fulfils its physiological function.

Axoplasmic Transport in Postganglionic Sympathetic Neurons

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The postganglionic neurons of the sympathetic nervous system, with the exception of those innervating the sweat glands, release noradrenaline at their terminals and may be described as noradrenergic (Dahlstrom, 1971). Noradrenergic neurons comprise perikaryon containing the nucleus, dendrites, axon and a terminal axonal network that ramifies the innervated tissue. The axon and its terminal network, containing the varicosities from which transmitter is

released, make up the bulk of the cytoplasm of the neurone. Despite their relatively great size, the axon and terminal network are dependent on their connexion with the much smaller perikaryon for their continued survival. Thus, after axotomy, the severed part of the axon and the terminal network degenerate whereas the axonal stump, joined to the neuronal cell body, can grow out to replace the lost structures. The reason for this dependence of the distant regions of the neuron on its cell body probably lies in the considerable synthetic capacity of the latter, especially with regard to proteins. Axons and their terminals appear to have, at best, a very limited ability to synthesize proteins. This dependence is not related to the electrical activity of the axon and thus implies that something, other than electrical impulses, passes from the perikaryon into the axon and its extremities. Indeed, as in other neurons, proteins pass along the axons of noradrenergic neurons in a centrifugal direction. Some of these proteins advance along the axon at a low rate (about 1 mm/day) whereas others travel at much higher rates (50–240 mm/day). Some of these latter proteins are known to be associated with sub-cellular particles and, so far as noradrenergic neurons are concerned, interest focuses on those particles storing noradrenaline. These intra-axonal particles, about 75 nm in diameter, can be recognized in the electron microscope by their electron-dense cores and are bounded by a lipoprotein membrane.

During the last 8 years it has become evident that the dense-cored vesicles containing noradrenaline are formed in the cell body, perhaps from larger precursors, and are transported along the axon to the terminal varicosities. There they are believed to contribute in some way to the population of small dense-cored vesicles (about 45 nm in diameter), which are probably the immediate source of the noradrenaline released in response to nerve stimulation. The amount of noradrenaline entering the terminal varicosities from the axon each day is only a small percentage of that lost by metabolism and released from the terminals during the same period. Hence it is not possible to regard the axonal transport of dense-cored vesicles as a device for keeping the varicosities filled with noradrenaline. This is largely accomplished by the synthetic enzymes present in the terminal network and by the recapture of released noradrenaline. Rather the proximodistal transport of dense-cored vesicles should be regarded as a means of keeping the varicosities supplied with noradrenaline-storage sites. During their passage along the axon these sites are probably only partially filled with noradrenaline and only achieve their final configuration and occupancy when they have arrived at their destination. The necessity for the replenishment of storage sites is, perhaps, a consequence of the gradual loss of vesicles. This would be a consequence of transmitter release by a process of