PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

Introductory Remarks

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Introductory remarks

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The proposal to have this meeting arose from biochemical studies. But we believe that the results obtained have wider implications in the field of physiology and cytology.

Biochemists have taken a part in the study of events occurring at the synapse ever since the transmitter theory was first enunciated. In fact, one of the first successes of the new theory was a biochemical one: the interpretation of the action of physostigmine as an inhibition of an enzyme, now called acetylcholinesterase (Loewi & Navratil 1926).

However, until recently the role of the biochemist in the study of synaptic transmission has been an ancillary one. He has provided information on the enzymic equipment of neurons, especially the equipment with enzymes involved in transmitter formation, and he has also studied transmitter inactivation.

But now, in the past year or two, the biochemists have also begun to share in the study of the events that occur during transmission.

These recent observations were made on adrenergic neurons. To the student of adrenergic systems the transmitter theory has been particularly relevant. The catecholamines have a dual function. In the chromaffin tissue they are secreted as true hormones, and at the endings of adrenergic neurons they are released as transmitters. It was this link that Dr Arnold Welch and I had in mind when we wrote the paper in which we described our early observations on chromaffin granules. We ended the discussion of this paper, dedicated to Otto Loewi on the occasion of his eightieth birthday, with the sentence: 'Such an interpretation would be in harmony with a concept that regards "secretion" from glandular tissue and "liberation" from nerves as events that are fundamentally related' (Blaschko & Welch 1953).

This idea of a fundamental relationship between chromaffin cells and adrenergic neurons has been strengthened by many observations since these words were written. The enzymes involved in the biosynthetic pathway were first studied in the adrenal medulla; subsequently their presence in adrenergic neurons was demonstrated. Also the cell organelles that carry the catecholamines were first isolated from the adrenal medulla; it was then shown that in adrenergic neurons also, there occur particulate elements that carry these amines.

Some of the proteins present in the chromaffin granules have been highly purified; this is true not only for enzymes but also for chromogranin A, the main soluble protein of the chromaffin granules, a compound for which a catalytic action has so far not been demonstrated. The functional significance of chromogranin has still to be discovered.

One has to use the adrenal medulla as starting material if one wants to obtain these proteins in sufficient amounts and in a reasonably high degree of purity. One can then prepare antibodies against them and look for them elsewhere, using immunological methods, for instance, in nervous tissue or in the effluents from stimulated tissues.

It was de Robertis who, on the basis of cytological observations, proposed exocytosis as the mode of release of the catecholamines from the adrenal medulla (see de Robertis 1964). You

will hear that this idea has received weighty support from biochemical studies. At the synapse exocytosis was first discussed by Katz (1962), in relation to the phenomenon of quantal release. He studied the neuromuscular junction, where the transmitter is acetylcholine.

The mention of cholinergic mechanisms reminds one of another important aspect, that of chemical specificity. Secreting cells and neurons liberate a host of different chemical messengers. In these tissues, therefore, we expect to find and indeed, do find, widely differing complements of compounds, together with their set of enzymes and possibly also with their different satellite proteins. In neurons, we exploit this chemical diversity in different ways, for instance by fluorescence microscopy of catecholamines or in immunological studies. Equally, I believe, we should be prepared to find functional, or morphological, differences in different kinds of neurons. When we try to formulate general rules governing transmitter release we should keep our minds open to the possibility that similarities are superimposed on diversities.

The work on adrenergic mechanisms, which has so clearly revealed similarities between chromaffin cells and adrenergic neurons, must also lead us to the question: What are the differences between glandular cells and neurons?

These differences, of course, must be in relation to intracellular *versus* extracellular distance. In the chromaffin cell intracellular distances are small in comparison with the extracellular distance that the chemical messenger has to travel after secretion, in order to reach the effector organ. In the neuron these relationships are reversed. Here the cell soma, the main centre from which biochemical processes are controlled, is separated from the site of release by the length of the axon. On the other hand, the extracellular distance that the messenger has to travel is minute. This occurs at the site of the synapse, the structure that chiefly interests us today.

One of the characteristic and distinctive properties of the neuron is the phenomenon of axonal flow, and this will be discussed today. And the student of adrenergic mechanisms also thinks of the phenomenon of re-uptake of transmitter. We might ask: is there perhaps a similar re-uptake process of satellite protein? So we have to find out what is known of protein uptake by neurons. There is also the possibility of protein uptake by the effector cell.

Catecholamines released as hormones find their way into the blood stream. We find the chromaffin cells situated close to the blood vessels. On the other hand, catecholamines released as transimitters reach the effector cells directly; the blood vessels are further removed from the site of release. These relationships must be borne in mind when differences in the yields of substances set free from these two tissues are encountered.

We remember that there exist neurons that do not end in a synapse. They release their chemical messengers as true hormones, at a distance from the effector cells. Such neurosecretory neurons are commonly found in invertebrates. In the vertebrates, there are the neurons that end in the posterior lobe of the pituitary gland. These are proper neurons, exhibiting normal electrical properties and axonal flow. And also here the chemical messenger is present in a cell organelle, accompanied by a satellite protein, neurophysin. In close analogy to the work on chromogranin, purification of neurophysin has preceded the study of its localization by immunofluorescence microscopy.

Finally, a word on the lines of research to which all these new findings point. If exocytosis, or a related event, is what happens when the messenger is set free, then the problems as to what distinguishes the cell at rest, or the neuron at rest, from the active one, resolves itself to the question: What is it that makes it possible for the membrane of the specific cell organelle that carries the messenger to attach itself to the cell membrane and maybe merge with it?

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The answer to this question will, I think, come from studies in which the combined skills of the physiologist, the biochemist and the cytologist have to be used.

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