Current Concepts in the Field of Neurochemical Mediation

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Chemical mediators involved in the integrative activities of the nervous system operate either at close range as neurohumors or over some distance as neurohormones. As will become evident, the distinction between neurohumoral and neurohormonal activities is not always clear-cut.

In "chemical synaptic transmission," the conventional mode of communication, messenger substances elicit strictly localized, postsynaptic responses of exceedingly short duration. Since the effector cells are contiguous with the respective presynaptic terminals, minute amounts of these substances are effective directly at the site of their release. Furthermore, at least in the case of adrenergic neurons, inactivation of the mediator immediately following the completion of the signal seems to be accomplished by a return of the active principle to its presynaptic storage site—through a "shuttle service" type of operation. Apparently the active principle can be used again and again, and the amount of mediator synthesized is, therefore, minimal in this case.

Messenger substances of this kind, such as acetylcholine and noradrenaline, lack essential features of endocrine factors—in particular, access to and use of vascular pathways. Therefore, they are appropriately classified as "neurotransmitters" or "neurohumors" rather than "neurohormones." The properties of this class of neurochemical mediators are so well known that they require no further discussion in this article.

Equally familiar by now are the ultrastructural attributes of chemical synapses, namely, the clusters of synaptic vesicles on the proximal side, the intersynaptic cleft with its content of variable electron opacity, and the asymmetrically arranged electron-dense deposits at the junctional membranes.

In addition to the synaptic transfer of signals, the conventional mode of communication, there exists another mode in which neural elements influence distant "targets" by means of a second class of chemical mediators. These substances have much in common with endocrine factors. They are not as speedily inactivated as neurotransmitters and do not seem to be used by the organism more than once. Furthermore, these special mediators reach multiple and diverse effector cells in appropriate concentrations by way of the circulatory system (Fig. 1). They can, therefore, be classified as neurohormones (B. Scharrer, 1969).

Sources of active principles with these properties are not as ubiquitous within nervous tissue as are those of the first group of chemical mediators. They form assemblies of highly specialized neurons which, instead of establishing synaptic contact with contiguous effector cells, terminate in close proximity to vascular channels. Because of the wide range of distribution of their

products, these neurons must engage in secretory activity to a degree that exceeds by far that of conventional neurons. Thus, this function becomes dominant. The high rate of synthetic activity is reflected by a decidedly glandular appearance closely resembling that of non-neuronal cells that produce the same kind of secretory products. Typically, these neuronally derived compounds are proteinaceous, another characteristic distinguishing them from the known neurotransmitters. In light microscopic preparations, the secretory products become conspicuous following selective staining procedures; in electron micrographs they appear as membrane-bounded, more or less electron dense granules in several characteristic size ranges.

Neurons of this special glandular kind have, therefore, been designated as "neurosecretory cells" and their products as neurosecretory material. It should be stressed that these terms were originally proposed solely on the basis of cytological criteria before a physiological explanation for the phenomenon of neurosecretion had been found. As it has turned out, the term "neurosecretory" has proved superior to other terms, such as "neurocrine" and "neuroendocrine," proposed at various times, since it encompasses activities that lie outside the realm of strictly neurohormonal phenomena. As will become evident later, these activities consist in the transfer of information at "neurosecretomotor" junctions.

Groups of axon terminals, in which neurosecretory substances are stored before being released, frequently form neurohemal organs, the best known of which is the posterior pituitary. These structures, together with corresponding intracerebral groups of neurosecretory perikarya, in which the active material is synthesized, constitute neurosecretory systems such as the hypothalamic-neurohypophysial system. The morphological complexity of these organ systems accounts for some of the difficulties that beset many early attempts to analyze the existing structure-function relationships.

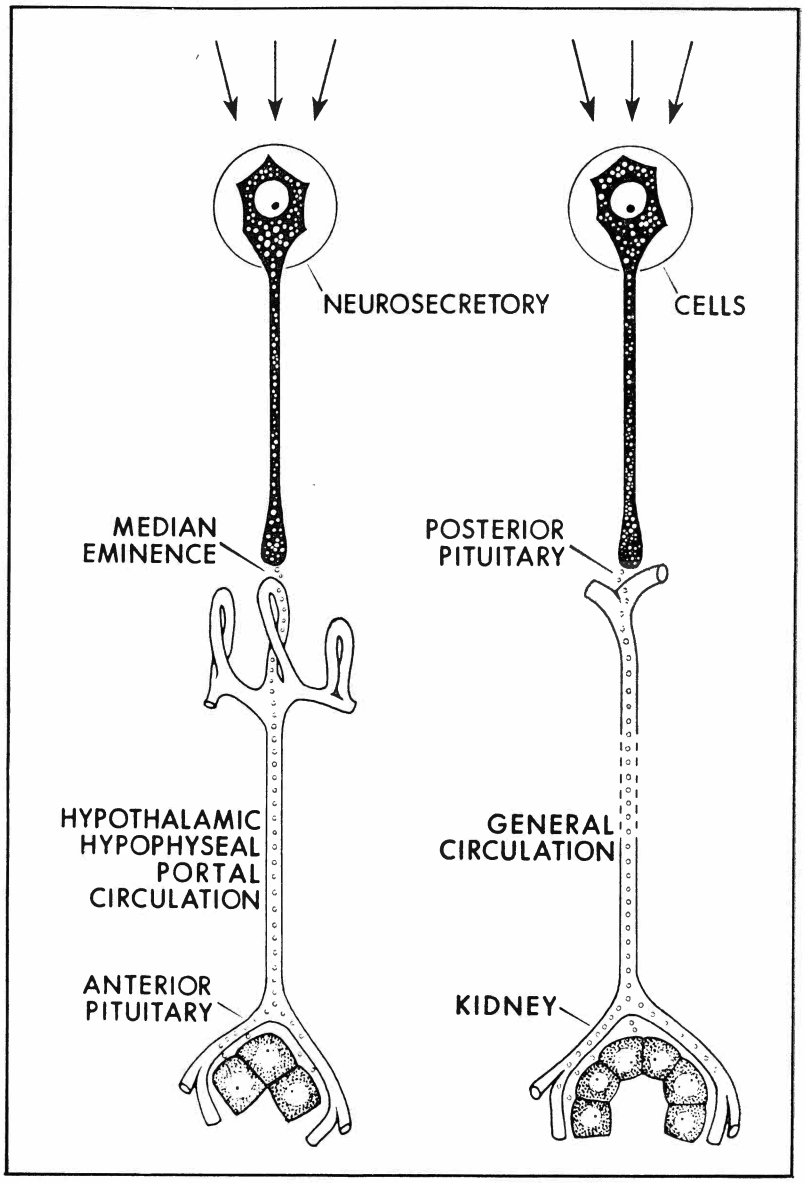

Fig. 1—Release of neurohormones from hypothalamic neurosecretory neurons occurs either in the posterior pituitary, from where they reach terminal target cells by way of the general circulation (right diagram), or in the median eminence of the neurohypophysis, where a special portal system carries neurohormonal signals to endocrine way stations in the adenohypophysis (left diagram). (Adapted from E. Scharrer, *Arch. Anat. Microscop. Morphol. Exp.* 54: 364, 1965.)

After a somewhat slow start and a good deal of opposition, the study of neurosecretory phenomena has made rapid advances in recent years. New insights have led to reevaluations of established data and to modulations in interpretation as well as terminology. There

is now an increased awareness of the theoretical and practical implications of this field of neurobiological research and its significance within the framework of neuroendocrine integration (E. Scharrer and B. Scharrer, 1963; B. Scharrer, 1967; Weitzman, 1964–69).

The remainder of my paper will focus on this special role. At this point it should be noted, however, that effector sites of neurohormones are not always endocrine cells. Rather, the hormone may act directly on "target" tissues such as uterine muscle or kidney tubules. Well-known examples of such first-order neurohormonal mechanisms are those controlled by the "posterior lobe hormones" vasopressin and oxytocin (Fig. 1, right).

The widespread occurrence of neurosecretory neurons in the animal kingdom bespeaks their basic function, that of providing a link between the nervous and the endocrine apparatus. In order to be effective, these two integrative systems must be capable of a high degree of interaction. Yet, each of them performs in its own characteristic manner. Signals from glands of internal secretion are conveyed to the nervous system by way of vascular channels and are known to be recorded by special "hormone-sensitive neurons." Messages in the opposite direction are handled in a more complicated manner, because regular nervous stimuli do not serve all of the requirements of the endocrine system. The need for sustained control mechanisms seems to be met best by signals of the same kind as those dispatched by the effector cells themselves, i.e., signals of hormonal nature. Therefore, the neurosecretory cell, which combines the properties of a neuron and a glandular cell, is made to order for this special task. It, and apparently it alone, is geared to receiving and processing information from neural centers and passing it on to the endocrine system in appropriate language (E. Scharrer, 1952, 1965, 1966). Typically, this mode of operation involves communication by means of neurohormones that reach their destinations in effective concentrations by way of either the general circulation or a locally restricted vascular pathway, such as the hypothalamic-adenohypophysial portal system.

Thus far, the distinction between conventional and neurosecretory neurons appears to be rather sharp. This is where matters stood before the advent of electron microscopy and other modern techniques. New research tools have restimulated in recent years interest in neuroendocrine problems, clarifying some areas of uncertainty while also pointing up new ones. In short, the "classical" view of neurosecretion is not the whole story.

Ultrastructural analysis of a variety of neurosecretory systems has revealed that not all of the terminals in which secretory granules

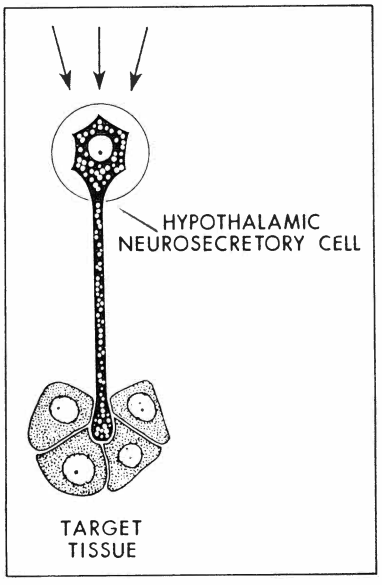

Fig. 2—Diagram of neurosecretory cell whose axon terminal makes close contact with endocrine effector cells. This hypothalamic neuron "translates" afferent signals (arrows) into chemical stimuli to which cells of the pars intermedia respond. An analogous situation exists in the corpus allatum of insects. (Adapted from E. Scharrer, *Arch. Anat. Microscop. Morphol. Exp.* 54: 363, 1965.)

are stored show direct association with the vascular system. Instead, some neurosecretory neurons display close spatial relationships with cellular elements. These are often endocrine, as, for example, those in the pars intermedia of the vertebrate pituitary and those of the corpus allatum of insects (Fig. 2). They may also be nonendocrine elements, such as some muscle cells in insects. In certain locations, processes of glial elements intervene between the axonal surfaces and various structures; in other locations direct contacts with other neurons seem to occur. In all these cases, the adjoining cells are often no further apart than are neurons at synaptic junctions; hence, the intercellular spaces measure roughly 200–300 Å (see B. Scharrer, 1968).

There are also somewhat transitional situations, in invertebrates as well as vertebrates, where the distances between neurosecretory neurons and adjacent non-neuronal cells are of the order of several thousand Å or more. These spaces are occupied by an acellular stromal matrix which seems to serve as a vehicle, and, possibly, also as a temporary reservoir, for the released substances.

Irrespective of the nature of the tissue components that face them, the terminals and some non-terminal areas of neurosecretory neurons show ultrastructural specializations resembling those of conventional presynaptic sites. These consist of clusters of small clear vesicles subjacent to the axolemma and certain densities affiliated with the junctional areas.

There is now a good deal of circumstantial evidence showing that these structural details are related to the mechanisms which release neurosecretory material from its intracellular storage site. The small vesicles with their electron-lucent contents appear to be the result of fragmentation occurring in the larger neurosecretory vesicles prior to the discharge of their

products. The diffuse dense material nearby gives the impression of having been spilled from the secretory vesicles. Most likely, it is neurosecretory material in transit. This means that the areas described appear to be release sites of neurosecretory substance which merely mimic synaptic elements but are not functionally equivalent to them. Their presence should not be interpreted as an indication of impulse conduction.

If the "synaptoid" areas just described do indeed serve this special purpose, it follows from their localization that not all of the neurosecretory material is destined for direct entry into vascular channels. Since some of these sites occur directly vis-à-vis adjoining cells, which may even show "postsynaptic" features, their arrangement cannot be merely coincidental. Especially in cases where such cells are part of an endocrine gland, viz., pars intermedia (Bargmann, Lindner and Andres, 1967), it is reasonable to conclude that they receive localized neurochemical stimuli at these "neurosecretomotor junctions." Under these special circumstances, the neurosecretory material cannot be called a neurohormone, because it acts directly at the site of release and does not reach the effector cell via the circulation. On the other hand, since the material is derived from a neurosecretory cell, rather than a conventional neuron, it does not qualify as a regular neurotransmitter either and should not be viewed in terms of standard neurohumoral regulation. It seems possible, although by no means certain as yet, that *in loco* activities of neurosecretory substances are concerned with inhibitory control, especially that of endocrine organs. There are two known cases in which severance of the nervous connection to the brain leads to activation of the respective endocrine tissue. These are the pars intermedia of vertebrates and the corpus allatum of insects. In both organs, neurosecretory fibers make contact with the glandular cell bodies.

Clearly, one is dealing here with intermediate situations that require further exploration before they can be properly evaluated. One conclusion can be drawn, however, from the observations made thus far. While it is still true that all neurohormones are derived from neurosecretory neurons, not all of the products of these special neuronal elements are endocrine in the strict sense of the word.

Comparative studies carried out in recent years have added yet another facet to existing views on neurosecretory activities. It appears that, in addition to the well-defined classical neurosecretory neurons, there are others in which the material to be discharged into the circulatory system or elsewhere is of non-peptide character. Such additional active principles produced "in quantity" are biogenic amines. Chemically, these can be compared to neurotransmitters operating in adrenergic neurons, but, functionally, they are more akin to the well-established neurohormones of polypeptide character. In fact, cells producing catecholamines for distribution via blood channels can be said to resemble classical neurosecretory neurons in all other respects except the chemical nature of their products.

Therefore, it has been tentatively proposed that a differentiation be made between classical ("peptidergic") neurosecretory A fibers and "aminergic" B fibers (Knowles, 1965; Bargmann et al., 1967). It must be stressed, however, that information on neurosecretory B fibers (not to be confused with the conventional neuron type for which the same letter is used in the neurophysiological literature) is still very incomplete.

The borderline between neurosecretory and conventional neurons must evidently be replaced by an intermediate zone for more than one reason. Neurosecretory neurons have turned out to be even more versatile than they appeared at the outset. They seem to be able to select, among several possible pathways, the one best suited for conveying each specific type of message required. They are not restricted to using one class of chemical mediator, and they can either function as intermediate links in neuroendocrine events that include a number of way stations, or they can take over the role of hormones effecting direct control over non-endocrine "terminal targets."

By comparison, the neurochemical interactions between conventional neurons and their effector cells follow a more uniform pattern, but here, too, some deviations exist. These refer mainly to special cases of sympathetic muscular innervation. Slow and relatively sustained signals to non-skeletal muscle fibers lacking neuromuscular junctions have to traverse a stroma-filled area whose diameter (as much as 2μ) is many times that of the regular intersynaptic gap (Barer, 1967). This arrangement compares precisely with the situation mentioned earlier in reference to special types of neurosecretory fibers. It is attractive to speculate that in both instances such mucopolysaccharide layers facing axonal surfaces may serve not only as vehicles but perhaps as extracellular storage sites for the respective neurochemical mediators.

Thus, it has become evident that deviations from the well-established functional patterns exist among neurosecretory, as well as non-neurosecretory, neurons. Both, then, contribute to that gradually emerging intermediate area which includes cells that do not conform to the standard types of either class of neurons. Further exploration of these variants will undoubtedly enrich the spectrum of neurobiology. However, new insights in this direction do not invalidate the existing differences in neurochemical mediation. The distinction between neurohumors and neurohormones remains conceptually important and should not be abandoned.

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