The Neurosecretory Neuron in Neuroendocrine Regulatory Mechanisms

BERTA SCHARRER

Department of Anatomy, Albert Einstein College of Medicine, New York, N.Y.

SYNOPSIS. The widespread occurrence of neurosecretory neurons in the animal kingdom suggests a functional significance that is basic and special. The explanation of the need for this unusual cell type lies in the fact that it forms a link between the nervous and the endocrine systems whose functional interdependence forms the basis for the effectiveness of regulatory mechanisms in the animal world. These two integrative systems function in different ways. The neurosecretory cell, with its dual characteristics, and this cell alone, seems capable of receiving messages in “neural” language, and of transmitting this information in modified “endocrine” language to glandular cells. The neurosecretory neuron occupies a central position in neuroendocrine interactions, not only because it is geared for communication with the endocrine apparatus, but because it serves as a singular channel (“final common path,” E. Scharrer, 1965) through which a multitude of afferent stimuli, after being processed, are channeled to a variety of endocrine way stations and thus exert control over their effector organs.

One of the most fertile concepts in the progress of endocrine research has been that of the functional interdependence of organs concerned with regulatory mechanisms. Under physiological conditions, individual glands of internal secretion do not function autonomously, but rather as links in an ever-changing sequence of events. In their entirety, these glands constitute the endocrine apparatus, one of the two integrative organ systems of higher organisms.

Environmental stimuli affecting the endocrine system reach it by way of the nervous apparatus, the other of the two systems of communication. Its makeup of innumerable links (neuron chains) is too well known to require discussion. What has not been fully appreciated, however, until very recently is the high degree of mutual interdependence that exists between the nervous and the endocrine systems. And yet, the situation could not be otherwise, because heterogeneous directives aimed at a given effector organ simultaneously, in order to be “effective” at all, must not contradict each other.

The manner in which the two integrative systems communicate with each other in coordinating the body’s autonomic adjustments, and the outcome of this combined activity, constitute Neuroendocrinology. This young, but rapidly expanding discipline encompasses many facets of mutual interaction (see Scharrer and Scharrer, 1963; Nalbandov, 1963; Bajusz and Jasmin, 1964; E. Scharrer, 1966; Weitzman, 1964-1966). Only some of these will be included in the following discussion whose central topic is the elucidation of the phenomenon of neurosecretion and its role in neuroendocrine integration. Even at that, current research contributions in this area are becoming so numerous that only a small selection of representative references can be given. These contain much of the documentation for the views expressed in the following pages and should be consulted for further orientation in this field.

If indeed nervous and endocrine components join forces by serving as alternating links in chains of regulatory activities, there must be means of communication between neurons and endocrine cells, and vice versa. Are the signals involved the same as, or different from, those used between two neurons, or two endocrine cells, respectively?

The type of chemical messenger (hormone) by which an endocrine cell communicates with either another endocrine or a “final target” cell (such as a uterine muscle fiber) can also serve for conveying information to a neural recipient. A well known example is the effect of circulating gonadal steroids on special cell groups in the mammalian hypothalamus, called “hormone-sensitive neurons.” These cells convert the information conveyed by such
stimuli into appropriate neural activity and elicit two types of response. One is a change in an animal’s behavior, as during estrus, the other is an endocrine event and involves, somewhere in the relay system, a step from neuron to endocrine cell.

Since the recipient cell is one geared to communication by chemical messengers, the switchover from nervous to endocrine system could well be accomplished by neurotransmitter substances (e.g., acetylcholine or noradrenaline) in a manner comparable to neurochemical events involved in “ordinary” synaptic transmission. This would require that axonal terminals conveying such information make direct contact with endocrine cells, since neurotransmitters are known to act in loco and to be destroyed promptly after having elicited a response. Only pinpointed signals of very short duration could, therefore, be involved and in this event every single endocrine cell would have to be “innervated.” There is no convincing morphological evidence for such an assumption, even though nerve terminals have now been shown, by means of electron microscopy, to establish close contact with parenchymal cells of at least some endocrine glands. The organs involved (pars intermedia of vertebrate pituitary, corpus allatum of insects) are, however, exceptional in that they represent parts of neurosecretory systems, which provide a special type of innervation (to be discussed below).

To reach the remainder of the endocrine system, nerve cells have to produce and release hormones which are better suited for the task at hand. By definition, hormonal mediators bridge distances and affect multiple instead of single target cells over a certain (often considerably sustained) period of time. Lacking these important characteristics, neurotransmitters do not qualify as hormones and should retain their separate status as neurohumors.

The postulate that neural elements engage in the manufacture of hormones was a bold departure from long established ideas. It is not surprising, therefore, that it met with a large share of persistent opposition. But after several decades of strife, the concept of neurosecretion is now firmly established, and its study has become a most active field in contemporary biological research. A brief characterization of the neurosecretory neuron may be in order before considering its special task of mediating between the two systems of integration.

THE NEUROSECRETORY NEURON AND THE CONCEPT OF NEUROSECRETION

The terms “neurosecretion” and “neurosecretory cell” were coined to denote the existence of a distinct class of neurons that engages in glandular activity to a degree above and beyond that observed in ordinary nerve cells. The claim for being singled out in this manner rests primarily on the fact that neurosecretory cells produce chemical mediators of hormonal character and are thus capable of dispatching signals to distant non-nervous centers by a vascular route.

The existence of neurosecretory activities was initially postulated on the basis of morphological information. Crucial tests of the validity of this concept have been provided by correlation of cytological knowledge with physiological and biochemical experimentation. Today, morphological research, by its extension to the ultrastructural level, has again moved into the limelight as an essential prerequisite for the solution of a number of problems still under dispute.

The subject of neurosecretion has been reviewed repeatedly (see Scharrer and Scharrer, 1968; for earlier references: Bern and Hagadorn, 1965; Picard and Stahl, 1966; Turner, 1966). A monumental volume on neurosecretion (Gabe, 1966) has now become available in English translation. The following summary of the characteristics of neurosecretory neurons can, therefore, be brief and focus on those aspects that are pertinent to our topic.

The neurosecretory cell is neither an ordinary neuron nor an endocrine cell, but a combination of both. Its neuronal features resemble those of ordinary neurons con-
cerning both structure and function. The production of a visible secretory material marks the neurosecretory neuron as a gland cell, and the fact that extractable cellular products act in the manner of hormones places it in the realm of endocrine elements.

The glandular products of “classical” neurosecretory cells are polypeptides (bound by a carrier protein, neurophysin) and thus differ chemically from known neurotransmitter substances. Neurosecretory material may be observed in both perikaryon and cellular processes. At the level of the light microscope, the demonstration of this intracytoplasmic material involves its selective stainability by methods such as Gomori’s chrome-hematoxylin phloxin and aldehyde fuchsin, Adams and Sloper’s alcian blue technique, and Schiebler and Sterba’s pseudoisocyanin-fluorescence method (Sterba, 1965).

In electron micrographs, neurosecretory cells can be recognized by the presence of membrane-bounded cytoplasmic granules of varying, but generally high, electron density and characteristic size ranges (frequently of the order of 1000 to 3000 Å). However, this characteristic should not by itself be considered as an absolute criterion. Evidence gathered from both light- and electron-microscopic investigation leads to the conclusion that neurosecretory substances are produced in the perikaryon. The ultrastructural “events” involved in their elaboration are virtually the same as those in other well documented cases of synthesis of proteinaceous glandular products, e.g., the zymogen granules of the exocrine pancreas. The material appears to be manufactured by the ergastoplasm (rough-surfaced endoplasmic reticulum) of the perikaryon and then to be “packaged” in the Golgi apparatus, where measured amounts are pinched off into the cytoplasm.

The neurosecretory granules are stored in the cytoplasm, apparently for varying periods of time, until their content is released. This may take place (at least in principle) at various levels of the neuron, e.g., the perikaryon. However, in most of the known neurosecretory centers, discharge occurs at the axon terminal. Neurosecretory granules reach this site by proximo-distal axonal transport. Evidence for the occurrence of this "migration" is conclusively provided by the accumulation of material at the proximal stump of the surgically interrupted pathway, and by the time sequence in the changing distribution of incorporated labeled precursors as determined by autoradiographic techniques (Flament-Durand, 1966).

A prominent characteristic of neurosecretory systems among invertebrates as well as vertebrates is the aggregation of bulbous, secretion-filled terminals around vascular channels; they form separate anatomical entities, called “neurohemal organs.” The best known examples of these storage depots are the neurohypophysis of vertebrates, the corpus cardiacum of insects, and the sinus gland of crustaceans. Furthermore, such neurosecretory systems commonly show an intimate relationship between the neurohemal organ and a non-neural endocrine structure (adenohypophysis of vertebrates, corpus allatum of insects).

The compact spatial arrangement of neurosecretory terminals in these neurohemal organs and the large amounts of stored material present make them well suited for histophysiological experimentation. Appropriate stimulation, such as prolonged thirsting in the rat for example, leads to a depletion of stored neurosecretory substance in the posterior pituitary, and rehydration induces a gradual re-establishment of “normal” stores of the physiologically active material.

The neurohormone released into the systemic circulation may affect an endocrine gland at some distance from the site of discharge (as in the control of the prothoracic gland of insects), or exercise direct control over an equally distant non-endocrine “terminal target” (such as the kidney cells concerned with water conservation). The latter case is an example of a first-order effect.

There is, among vertebrates, also a more “exclusive” vascular route by which neurohormonal stimuli may reach their desti-
nations. The hypophysial portal system channels “hypothalamic releasing factors” to endocrine cells of the anterior pituitary. Here the results are either second- or third-order neuroendocrine events (with one or two endocrine centers interposed).

A third possibility for the nervous system to reach endocrine targets has been mentioned earlier and is exemplified by the control mechanism over the pars intermedia and the corpus allatum. It is the most “directed” among the existing pathways, and involves close contact between axon terminals and endocrine cells (secretomotor junctions). When the gap between axolemma and plasma membrane of an endocrine cell at such a junction is sufficiently small (of the order of 200-300 Å), a neurohumoral mode of transmission is feasible. This certainly applies to cases of innervation of gland cells by non-neurosecretory fibers (Picard and Stahl, 1966).

It is unknown whether or not neurotransmitter substances play a comparable role when endocrine cells are affected at equally close range by neurosecretory fibers (see Polenov, et al., 1965). Since their terminals, like those of ordinary axons, contain small, clear (“synaptic”) vesicles, a morphological basis for such activity exists. However, it seems more likely that the neurosecretory cell makes use of its special chemical endowment for eliciting responses from the effector cell, irrespective of the distance involved. Cases in point are the pituitary of fishes (Knowles and Vollrath, 1966a, b) and probably the prothoracic gland of insects (B. Scharrer, 1964), organs of internal secretion that are “innervated” by neurosecretory fibers. In both instances, extracellular gaps (around 3000-4000 Å) have been observed exceeding those characteristic of synapses. The neurosecretory terminals need not, and here evidently do not, approach target cells quite as closely as would be required for ordinary synaptic contact. Consequently, the small, clear vesicles present in neurosecretory terminals must be interpreted as playing a role different from that of regular synaptic vesicles, a role most likely concerned with the release mechanism of neurosecretory products, to be discussed shortly.

Little is known about a possible fourth vehicle for the conveyance of neurosecretory material. Various light- and ultramicroscopic data suggest a release into the cerebrospinal fluid. The functional significance of this phenomenon is difficult to assess. It has been suggested (Fridberg and Nishioka, 1966) that neurohormone extruded into the third ventricle or central canal may become absorbed by the choroidal plexus and then reach target organs by vascular transport. There may also be effects of neurosecretory substances distributed by the cerebrospinal fluid on nerve centers other than those in which these hormones originate.

There is still much uncertainty as to what constitutes the stimulus for the liberation of neurosecretory material from its intraneuronal storage site. Are the signals for discharge provided by the same neuron, or do they have to come from a separate neuron with which the neurosecretory fiber is in direct contact? (See, for example, Heller and Ginsburg, 1966; Sloper, 1966.) A closely related and similarly vexing question concerns the form in which the active principles are released into the extracellular channels. There are indications for several possibilities, but none of them has been satisfactorily proved. On morphological grounds, it seems unlikely that membrane-bounded granules enter the circulation in intact form. Probably the shell is left behind when the active polypeptides, with or without their carrier protein, are liberated from the neurosecretory terminal. Some investigators, therefore, interpret the “synaptic vesicles” in these terminals as remnants of neurosecretory granules from which part or all of the content has been discharged. Others hold that their presence signifies a role of acetylcholine in the liberation of the active polypeptides, presumably by altering membrane-permeability.

Since the neurosecretory neuron is capable of conducting impulses, the signal for the release of polypeptide hormones could
well be given by the same cell that furnishes these substances. But there is also evidence for an alternative solution of this problem.

Currently, considerable attention is being given to the interpretation of existing "synaptoid" contacts between "classical" neurosecretory fibers (A fibers of Knowles, 1965) with polypeptide-containing granules of more than 1000 Å and axons with membrane-bounded electron-dense granules of somewhat different appearance and a diameter of less than 1000 Å (B fibers of Knowles; see also B. Scharrer, 1963, and Fig. 1). These B fibers may influence the release of peptide neurohormones from terminals of A fibers in neurohemal organs of vertebrates and invertebrates.

It appears that B fibers that terminate at capillaries of the median eminence (Rinne and Arstila, 1965-66; Monroe, 1966, and others) play an essential role in the control of adenohypophysial functions, either by monitoring the discharge of hypothalamic "releasing factors" of polypeptide nature, or perhaps by themselves supplying one or more releasing factors. The latter possibility has been explored, for example, by the examination of existing relationships between changes in the dopamine content of tubero-infundibular B fibers and specific events in the reproductive physiology of rats (Fuxe, et al., 1966b).

B-type fibers seem to belong to a class of neurons that are rich in monoamines. Their existence can be demonstrated by a technique utilizing highly specific histochemical fluorescence (Falck, et al., 1962, 1965). However, there is as yet no certainty about the precise intracytoplasmic localization of the catecholamines involved. Current views associate them with small vesicles of the "synaptic" type rather than with the small dense-core granules mentioned above. Such clear vesicles are numerous not only in the axon terminals but also in the perikaryons of B-type neurons, and their
distribution parallels the sites of formation and/or storage of catecholamine as determined by the fluorescence-technique (Fuxe, et al., 1966a).

If it can be established that physiologically active catecholamines released from neurons reach target cells by a vascular route, such as the hypophysial portal system, these catecholamines would then qualify as neurohormones. In this event, their cells of origin would become established as another class of neurosecretory neurons whose major difference from the classical prototype would be the non-polypeptide character of their physiologically active secretory products. In short, chemical considerations in the characterization and classification of neurosecretory systems may have to undergo modification.

The existence of more than one class of neurosecretory neurons had been detected earlier, at the light-microscopic level, on the basis of different tinctorial affinities. The well established common variety, whose secretory products stain with chrome hematoxylin or aldehyde fuchsin, seems to correspond to the A fibers observed in electron micrographs. On the other hand, neurosecretory neurons with staining properties different from those of "classical" A fibers, may turn out to belong to class B fibers and may fulfill functions of a special kind, in particular those involving short term activities.

In summary, the development in recent years of more sophisticated methods involving high resolution microscopy and cytotopochemistry has provided answers to questions for which earlier microscopic techniques had been inadequate. At the same time, this deeper penetration into the phenomenon of neurosecretion has opened up new problems. The establishment of valid criteria for neurosecretory neurons has undergone changes (see Knowles and Bern, 1966), but some uncertainty remains concerning the precise borderline between ordinary and neurosecretory neurons. Further modulations of our concepts will undoubtedly occur, but the special status of the neurosecretory neuron within the rest of the nervous apparatus is now firmly established.

THE SPECIAL ROLE OF THE NEUROSECRETORY NEURON IN NEUROENDOCRINE INTERACTIONS

We may now return to the cardinal question, i.e., the reason for the existence of neurosecretory neurons. Their widespread occurrence in the animal kingdom suggests a functional significance that is basic and special. The explanation of the need for this unusual cell type lies in the fact, already touched upon earlier in this text, that the two integrative systems function in different ways. In the nervous tissue, we have primarily a point-to-point transmission of signals with a duration of the order of fractions of a second. In the

![Diagram illustrating theoretically possible neuroendocrine interactions. Both nervous and hormonal signals are symbolized by arrows. In any given case of a function under neuroendocrine control, in any particular animal, only some of the pathways are actually used. (Reprinted from Scharrer and Scharrer, 1965, Neuroendocrinology, Columbia University Press, New York.)](https://academic.oup.com/icb/article-abstract/7/1/161/168831)
endocrine system, there occurs a much slower and much less directed transmission of messages. The neurosecretory cell with its dual characteristics, and this cell alone, seems capable of receiving messages in "neural language," and of transmitting this

![Diagram](https://academic.oup.com/icb/article-abstract/7/1/161/168831)

**FIG. 3.** Neurosecretory cells acting as mediators between nervous and endocrine systems. The diagram illustrates the relationship for the prototype of a neuroendocrine integration center, the hypothalamus of higher vertebrates. (Reprinted from Scharrer and Scharrer, 1963, Neuroendocrinology, Columbia University Press, New York.)
information in modified "endocrine language" to a glandular cell (E. Scharrer, 1952).

Now that this crucial point has been elucidated, we can present a scheme for all of the theoretically possible interactions between neural and endocrine factors. A diagram (Fig. 2) shows how various afferent stimuli from the internal and external milieus enter central circuits that link the neural and endocrine components of the integrative apparatus, and how efferent signals from endocrine centers reach "final targets."

The neurosecretory neuron occupies a central position in all of these interactions, not only because it is geared for communication with the endocrine apparatus, but because it serves as a singular channel ("final common path," E. Scharrer 1965, 1966) through which a multitude of afferent stimuli after being processed reach a variety of endocrine way stations (Fig. 3).

This common pathway is more constant than the rest of the possible connections diagrammed in Fig. 2. Among the latter, various suitable combinations may be in operation depending on the type of physiological process, or the animal species, or other variable factors we happen to be dealing with. A detailed documentation of this basic scheme may be found in the text by Scharrer and Scharrer (1963). Here a brief survey of two representative examples may serve to illustrate the principle.

One concerns mammalian reproduction where the control mechanism of the cyclic events in the female requires a complex combination of signals. Among a variety of conditioning factors entering the central circuits are extrinsic sensory (olfactory, visual, etc.) signals, afferent endocrine stimuli (including gonadal feedback), and information coming from peripheral effector organs such as the uterus. Under the influence of neurohormonal "releasing factors" (see Harris, et al., 1966), several types of gonadotropic hormones are successively withheld or released according to a precise time schedule. The programming of these hormones in turn guarantees cyclic events in the ovary with periodic consequences in peripheral target organs, especially the uterus.

Another example of complex neuroendocrine interaction is the control of insect development. Growth and metamorphosis depend on gradual shifts in the relative importance of two interacting hormonal centers, the prothoracic gland and the corpus allatum. Here the central nervous system not only governs the cyclic performance of each individual gland, but apparently also serves to correlate the simultaneous activities of both. The integrative center in question is part of the protocerebrum. By means of a blood-borne neurosecretory principle, it stimulates the release of the molting hormone, ecdysone, from the prothoracic gland, and by direct nerve supply (at least part of which is neurosecretory) it regulates the amount of juvenile hormone furnished by the corpus allatum. Only by coming from the same source can these neural signals for two chains of command guarantee the proper adjustments between both parallel endocrine activities during each of the consecutive developmental steps.

SUMMARY

The functional interdependence of the nervous and endocrine systems forms the basis for the effectiveness of regulatory mechanisms in the animal world. An important link between these two integrative systems is provided by a class of cellular elements with dual capacities, the neurosecretory neurons. Through these intermediaries a multiplicity of signals, received and processed by the nervous system, are channeled to endocrine centers to exert control over their intricate functions.

REFERENCES


