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FORTY-SEVENTH
JAMES ARTHUR LECTURE ON
THE EVOLUTION OF THE HUMAN BRAIN/

AN EVOLUTIONARY INTERPRETATION
OF THE
PHENOMENON OF NEUROSECRETION

BERTA SCHARRER

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- *John Z. Young, *What Squids and Octopuses Tell Us About Brains and Memories*, May 13, 1976
- *Berta Scharrer, *An Evolutionary Interpretation of the Phenomenon of Neurosecretion*; April 12, 1977

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AN EVOLUTIONARY INTERPRETATION OF THE PHENOMENON OF NEUROSECRETION

INTRODUCTION

Almost 50 years ago, Ernst Scharrer (1928) made a discovery that was received by the scientific community with great skepticism, if not with outright rejection. It marked the beginning of a scientific adventure that has given rise to one of the most challenging pursuits in neurobiological research, the results of which have been dramatic. Based on cytological observations in a teleost fish, *Phoxinus laevis*, he postulated that certain groups of distinctive cells in the hypothalamus ("neurosecretory neurons") engage in secretory activity to a degree comparable to that of endocrine gland cells. He further suggested that this activity may be related to hypophysial function.

A search in the literature yielded but one comparable report calling attention to the occurrence of "glandlike" nerve cells in another part of the central nervous system, the spinal cord of skates (Speidel, 1919). Subsequent studies demonstrated the almost ubiquitous occurrence of such neurons throughout the animal kingdom. Yet, for many years to come, the spotlight remained on the hypothalamic neurosecretory centers of the vertebrate series. The elucidation of their close affiliation with the pituitary gland eventually gave rise to a new discipline, neuroendocrinology.

However, recognition of these unusual neural elements represents a challenge to the neuron doctrine, according to which nerve cells are most commonly thought of as being designed for the reception of stimuli, the generation and propagation of bioelectrical potentials, and the rapid, synaptic transmission of signals to contiguous recipient cells. "Conventional" neurons make only very restricted use of chemical mediators in the form of special neurotransmitters and certain other regulatory substances.

In contrast, the primary activity of the classical neurosecretory cell consists of the manufacture of a distinctive (proteinaceous) product in sufficient quantity to function in a hormonal capacity. Furthermore, its axon terminates, without establishing synaptic contact, in close proximity to the vascular system. No wonder that, because of these "aberrant" attributes, neurosecretory phenomena were long looked at askance and frequently brushed off as signs of degenerative or postmortem changes. Today, this mistrust no longer exists, as will become apparent in the following discussion.

An important step forward was the demonstration that the "posterior lobe hormones," e.g., vasopressin, are derived from peptidergic neurosecretory nuclei of the hypothalamus and are transported by axoplasmic flow to the posterior pituitary where they are released into the general circulation (Bargmann and Scharrer, 1951). At last, the endocrine nature of some of these neuroglandular elements had been established.

But even then a vexing question remained. Why should the body make use of nerve cells to provide hormonal messengers in order to reach terminal effector sites such as the kidney? This conceptual difficulty stems from the established custom of classifying neuroregulatory and glandular functions as two distinctly separate categories. In reality, there are cogent reasons for bridging this gap, based largely on evidence that is implicit in the evolutionary history of integrative systems.

PHYLOGENY OF NEURAL SYSTEMS OF COMMUNICATION

A careful consideration of the phylogenetic, and to some extent the ontogenetic, development of such informational systems has made it increasingly clear that the manufacture and release of secretory products is an old and fundamental attribute of neuronal elements. The evolutionary approach, featured in this article, is based on the premise that the most elementary integrative mechanisms existing today may resemble those of our remote ancestors (Pavans de Ceccatty, 1974).

By reason of its phylogenetic derivation from a pluripotential epithelial element, the primitive nerve cell can be viewed as a

functionally versatile structure, endowed with the capacity to dispatch both long distance and localized chemical signals. This concept is supported by a substantial body of information on neuroregulatory mechanisms encompassing all multicellular animals (see Lentz, 1968; Highnam and Hill, 1977). Starting with the simplest forms among them, we find in sponges a reticular neuroid tissue complex whose components do not yet satisfy all the criteria of nerve cells. The first primitive neurons with elementary synaptic contacts appear in the lowest eumetazoans, the coelenterates.

What seems important in the context of the present analysis is that in both groups some of the cells mentioned display cytological signs of neurosecretory activity. The cytoplasmic granules observed here are comparable to those of higher animals in that they stain with alcian blue and, in electron micrographs, appear electron dense and membrane-bounded with diameters of 1,000-1,700 Å (Pavans de Ceccatty, 1966; Lentz, 1968; Davis, 1974). Neurosecretory granules are abundant in the nervous system of planarians. In the ganglia of annelids more than one-half of all neurons are of the neurosecretory type.

Even more relevant is the fact that distinctive hormonal functions as well as other "nonconventional" neuroregulatory roles can be ascribed to the neurosecretory neurons of these lower invertebrates. Tests with isolated neurosecretory granules of the coelenterate *Hydra* reveal that their content regulates growth and differentiation, especially during regeneration (Lentz, 1968). This neuromediator also seems to participate in the induction of gametogenesis and sexual differentiation (Burnett and Diehl, 1964). Similarly, neurosecretory control, over a distance, of growth during development and regeneration and of certain reproductive events has been demonstrated in planarians (Lentz, 1968; Grasso and Benazzi, 1973) and in annelids (Hauenschild, 1974).

The salient point is that in none of these primitive invertebrates have "regular," i.e., nonneural glands of internal secretion been identified. Therefore, at this level of differentiation, the nervous system seems to be the only agency available for carrying out all of the existing endocrine functions. Neurohormones thus hold the

rank of the phylogenetically oldest integrative long-distance messengers, and the endocrine type of coordination accounts for a relatively large sector of neuronal activities in lower invertebrates. In other words, far from being a latecomer and a rare exception, the neurosecretory neuron dates back to the very beginning of the development of neural structures. Furthermore, its versatility indicates that it has remained closer to the nerve cell precursor than has the more specialized "conventional" neuron.

In the course of evolution the scene shifts in more than one direction. Not only is there a staggering increase in the number of neurons, as primitive nervous systems give way to more and more elaborate structures but, in the most advanced forms, the vast majority of "conventional" nerve cells engage in interneuronal synaptic transmission involving the release of tiny, precisely metered amounts of chemical transmitter substances. Some of these special messengers are used over and over again. Therefore, in these billions of neurons, the demands for secretory activity have become greatly reduced.

Another, equally important, evolutionary change in design is the evolvement of extraneuronal hormone sources. The structural and functional attributes of the endocrine apparatus have long been thought to be as clearly defined as have those of neurons. Yet, the dividing line is by no means complete, on account of the neuroectodermal origin of peptide-producing endocrine cells to be discussed below. According to this concept (Pearse, 1976), the relationship between the neuronal and nonneuronal hormone sources of the hypothalamic-hypophysial complex is even closer than formerly recognized, since both share their origin from the same precursor cells in the ventral neural ridge. However, in spite of this embryonic background, the cells of the adenohypophysis should not be classified as neural elements. They have crossed over to join the ranks of the endocrine system. This process of metamorphosis entails the loss of structural and cytochemical neural attributes and the acquisition of endocrine qualities which these polypeptide-hormone-secreting cells share with the rest of the endocrine apparatus.

The evolvement of this second integrative system that specializes in hormonal communication, making use of various types of

chemical messengers, argues against the need for blood-borne neurochemical mediators in higher animals. Quite obviously, its existence should relieve neurons from doing double duty.

NEUROENDOCRINE INTERACTIONS

In reality neurohormones do not become obsolete after the acquisition, by arthropods and vertebrates, of an endocrine apparatus proper. Instead they take over a novel and highly significant role, that of mediation between the two systems of integration. As has been pointed out repeatedly in the past (Scharrer, 1970-1974), the neurosecretory neuron, having retained its dual capacity, is ideally suited and programmed for this special task.

In view of this shift in functional significance, the question raised earlier, concerning the *raison d'être* of first-order neurohormonal mechanisms even in the most highly developed organisms, now appears in a different light. Such one-step systems, e.g., the control of water metabolism by vasopressin, have certainly become overshadowed by those constituting the all-important neuroendocrine channel of communication. They do not even seem to be obligatory. Yet, their existence makes sense in an evolutionary perspective, i.e., when interpreted as carryovers from systems operating by necessity in phylogenetically less advanced forms.

NONNEUROHORMONAL PEPTIDERGIC ACTIVITIES

A rather unexpected and challenging result of the detailed ultrastructural analysis of the neuroendocrine axis in vertebrates and invertebrates was the realization that not all the neurosecretory neurons dispatch their messenger substances via the general or the special portal circulation. There are, in fact, several recognized modes of neurochemical communication that are neither strictly neurohumoral (synaptic) nor neurohormonal (blood-borne). One such mechanism is the long known regulation of tissue growth and maintenance, by "neurotrophic substances" (see Smith and Kreutzberg, 1976). The chemistry and extracellular pathway of these diffusible substances released from sensory and motor fibers are still uncertain.

Information on nonvascular extracellular avenues available to peptidergic neurosecretory messengers is more precise. These variants include the cerebrospinal fluid (see Rodríguez, 1976), zones of extracellular stroma, and even narrow "synaptoid" gaps. Axons laden with neurosecretory material can be observed to penetrate the glandular parenchyma of the adenohypophysis as well as the corpus allatum of insects. In both organs synaptoid release sites occur in close vicinity to, or even in contiguity with, their apparent cells of destination. Furthermore, such spatial relationships are not restricted to endocrine elements, but are also found in a variety of somatic structures, among them various exocrine gland cells and muscle fibers.

Perhaps the most unexpected informational systems are those in which neurosecretory neurons establish synapse-like relationships with other neurons, some of which may themselves be of the nonconventional type (see Scharrer, 1976). The realization that, at least in certain special situations, peptidergic neurosecretory mediators may operate in a manner comparable to that of neurotransmitters has added a new and important facet to the "gestalt" of the classical neurosecretory neuron. The existence of these several intermediary possibilities for the transfer of information by neurosecretory cells has clarified their relationship with the more conventional neuronal types. Consequently, the sharp dividing line originally thought to separate conventional from classical neurosecretory neurons no longer exists. Now the modes of operation of classical neurosecretory neurons actually blend into a continuum of diverse neurochemical activities.

NONCONVENTIONAL INTERNEURONAL COMMUNICATION

What makes the discovery of synaptoid structures between neurons intriguing is that they go hand in hand with increasing physiological evidence in support of the concept that nonconventional (peptidergic) neuroregulators may modulate certain forms of synaptic interneuronal communication. This broader neurotropic activity will undoubtedly turn out to represent a novel and important form of information transfer with far-reaching biomedical implications (see, for example, Constantinidis et al.,

1974; Sterba, 1974; Brown and Vale, 1975; Plotnikoff et al., 1975; Prange et al., 1975a, 1975b; Vincent and Arnauld, 1975; Brownstein et al., 1976; Guillemin, Ling and Burgus, 1976; Lote et al., 1976).

To cite an example of such known activities among the hypophysiotropic hormones, or factors, TRF (thyrotropin releasing factor) has a modulating effect on synaptic, especially monoaminergic, transmission. Apparently, this role evolved before that of controlling thyrotropin release, and it seems to be of a more general importance (Grimm-Jørgensen, McKelvy and Jackson, 1975; McCann and Moss, 1975; Waziri, 1975; see also Nicoll, 1977). A broader role for the posterior lobe hormone vasopressin, or fragments thereof, is that demonstrated by de Wied and his co-workers (1976) and involved in the control of various forms of behavior. Moreover, effects that differ from conductance changes evoked by conventional neurotransmitters can be elicited in certain neurosecretory neurons of molluscs by the application of vasopressin and related peptides (Barker and Gainer, 1974). Finally, there is new and intriguing evidence that two specific neuronal pentapeptides (enkephalins, Hughes et al., 1975) function as endogenous analgesics presumably by suppressing excitatory synaptic signals implicated in the perception of pain (see Snyder, 1977).

BIOCHEMICAL EVOLUTION OF NEUROSECRETORY MEDIATORS

The evolutionary interpretation of the phenomenon of neurosecretion presented here is not based on morphological and physiological evidence alone. It can be further substantiated by tracing the biochemical history of neurosecretory mediators, even though the picture is still incomplete.

Among the general trends that are beginning to emerge are the following. In contrast to those used in much smaller amounts by conventional nerve cells, the chemical messengers operating in classical neurosecretory neurons of both vertebrates and invertebrates are proteinaceous in nature. Furthermore, the biologically active polypeptides of many neurosecretory neurons are bound by

noncovalent forces to special carrier proteins, called neurophysins (see Walter, 1975; Watkins, 1975; Acher, 1976b), which are primarily responsible for the selective stainability of neurosecretory material throughout the animal kingdom. Aside from serving as carrier molecules, these proteins may play an active role of their own (Pilgrim, 1974).

Much information is being amassed on the occurrence and precise localization of such neuropeptides and their affiliated neurophysins within the neurosecretory systems of a variety of animals by the use of immunochemical, especially immunoelectron-microscopic methods (see McNeill et al., 1976; Ude, 1976; Zimmerman, 1976). In addition, synthetically produced neurohormones and their analogs are becoming available in increasing numbers. These advances offer valuable tools for the differential determination of the relationships and functional roles of these substances.

There is substantial support for the concept that the characteristic products of presently existing neurosecretory neurons have a common evolutionary origin. Gene duplication, modification, and cleavage of ancestral proteinaceous molecules are presumed to have been involved in the development of chemical entities with more and more diversified functional properties (see Wallis, 1975).

This process seems to be reflected by the fact that enzymatic dissociation is responsible for the biosynthesis of most, if not all, biologically active peptides known today (Tager and Steiner, 1974; Acher, 1976b). For example, the active nonapeptides stored in the mammalian posterior lobe and the corresponding carrier proteins are apparently not synthesized as such in the perikarya of the respective hypothalamic neurons but are cleaved from a precursor of higher molecular weight (Sachs et al., 1969; Gainer, Sarne and Brownstein, 1977). The fact that both components make a strikingly sudden and simultaneous appearance early during fetal development (Pearson, Goodman and Sachs, 1975) supports the view that they share the same macromolecular precursor. Moreover, the impressive structural similarity throughout the entire vertebrate series of neurohypophysial hormones (Heller, 1974; Carraway and Leeman, 1975; Wallis, 1975; Acher, 1976a)

as well as their corresponding neurophysins (Capra and Walter, 1975; Acher, 1976b; Zimmerman, 1976) suggests that their present precursor molecules (prohormones) are derived from closely related ancestral proteins.

The same type of lineage can be claimed for hypophysiotropic factors, the amino acid sequences of which are contained in parent compounds of higher molecular weight. For example, nonapeptides with hormonal activities of their own can play the role of precursor for short-chain principles, such as the tripeptide MIF (MSH-release inhibiting factor, melanostatin), a neurohormone with different functional capacities (Walter, 1974; Reith et al., 1977). Parenthetically, another unexpected feature about nonapeptides is the recently reported presence of vasopressin, unaccompanied by neurophysin, in a cell line from a human lung carcinoma (Pettengill et al., 1977).

Information on analogous proteinaceous compounds in invertebrates is still sporadic. Nevertheless, histochemical and biochemical parallelisms can be recognized. For example, a chromatophorotropin that was chemically identified in crustaceans shows a close resemblance to some of the small hypophysiotropic peptides of mammals (Fernlund and Josefsson, 1972; Carlsen, Christensen and Josefsson, 1976). Furthermore, a chemically synthesized octapeptide was shown to elicit pigment concentration in two types of crustacean chromatophores *in vitro* and *in vivo* (Josefsson, 1975). A similar fully identified neuropeptide is the adipokinetic hormone of insects (Stone et al., 1976). Another case in point is the recent demonstration of immunoreactive TRF (thyrotropin releasing factor) in the ganglia of some gastropods (Grimm-Jørgensen, McKelvy and Jackson, 1975) where, for obvious reasons, its function could resemble only the extrahypothalamic activities demonstrated in vertebrates. An indication of the occurrence of such nonconventional interneuronal communication is the recent observation (Takeuchi, Matsumoto and Mori, 1977) that certain neurons of the snail *Achatina* are differentially affected by fragments of some enzymatically treated nonapeptides, e.g., oxytocin and vasotocin.

Finally, are there common denominators in the biosynthetic and functional features of classical neurosecretory materials and

of other biologically active peptides produced by neurons and/or glandular elements derived from neuroectodermal precursors (anterior pituitary and other members of the APUD cell series, Pearse, 1976; Pearse and Takor Takor, 1976)?

In underscoring the neuroembryological and cytochemical features shared by these cells, Pearse's intriguing concept clarifies the multiple occurrence, both within and outside the adult nervous system, of a variety of regulatory peptides, including Substance P, enkephalins, endorphins, and several hypophysial hormones. Therefore, all of these peptides may also have in common the mode of their molecular evolution.

An example in support of this proposition is the mounting evidence for the derivation of several such peptides with distinctive physiological properties from a larger parent molecule, the formerly enigmatic pituitary hormone β -lipotropin (Li, 1964). Among its subunits the endorphins (Goldstein, 1976; Guillemin, 1977) are currently receiving much attention because of their analgesic and behavioral effects. The N-terminal of α -endorphin, a short sequence (amino acid residues 61 through 65) apparently representing the analgesically active core, precisely matches that of methionine enkephalin, one of the two specific neuronal pentapeptides already referred to (Cox, Goldstein and Li, 1976; Guillemin, 1977; Guillemin, Ling and Burgus, 1976). Therefore, these endogenous opiates could be generated from the prohormone β -lipotropin, either within the brain or in the pituitary, in which case they could reach their sites of action via the circulation or the cerebrospinal fluid (Reith et al., 1977).

There are also several indications of functional parallelisms. One is the demonstration that, in company with several hypophysiotropic polypeptides, enkephalin and endorphin (Dupont et al., 1977; Simantov and Snyder, 1977) as well as Substance P (Kato et al., 1976) elicit the release of growth hormone, ACTH, FSH, and prolactin. Another is that Substance P, like enkephalin, endorphin, and several hypophysiotropins, may act as a modulator of neuronal activity (see Zetler, 1976).

Neither enkephalins nor opiate receptors have thus far been found among invertebrates (Snyder, 1977). Nevertheless, the features that all the biologically active peptides known to date have

in common add up to the following generalization. In the course of a long evolutionary history, ancestral macromolecular proteins have given rise to a variety of related compounds. Multiple sites of cleavage and molecular modulation seem to have resulted in the acquisition and dissociation of diverse, e.g., hormonal, neurotransmitter-like, and carrier functions, whereby one active principle may act in more than one capacity. These possibilities, borne out by phylogenetic and ontogenetic considerations, illustrate the principle of biochemical economy.

CONCLUSIONS

An examination of the evolutionary history of neural tissue, and its pluripotentiality in primitive animals, points up its special glandular attributes. The old inherited capacity for secretory activity seems to have been put to use in multiple and specialized ways at consecutive levels of the evolutionary scale. Therefore, the spectrum of available neurochemical mediators and of modes of information transfer that digress from standard synaptic transmission is more diversified than previously assumed, even in higher forms. Hormones derived from neural elements have remained indispensable even after the appearance of the endocrine system proper. The most unorthodox neurosecretory cells giving rise to these blood-borne proteinaceous messengers, as well as those signaling at closer range, have found their place within the range of existing variants. Now that the versatility of the hypothalamic neurosecretory centers and their major role in neuroendocrine integration have been clarified, current interest can turn to extrahypothalamic neuropeptides. This nonconventional minority seems to have a relatively wide distribution within and outside the central nervous system and to function in remarkable ways. Further exploration of the glandular aspects of neuronal function and their relationship with peptide-hormone-producing cells of neuroectodermal origin holds much promise.

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