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HISTORICAL NOTE ON THE DEVELOPMENT OF THE CONCEPT OF THE HYPOTHALAMIC "RELEASING FACTORS"*

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Summary

A short account is given on the various concepts and converging interdisciplinary approaches which eventually led to the definition and identification of hypothalamic releasing and release-inhibiting factors. A classification of neuro-endocrine systems is also proposed.

Zusammenfassung

Es wird ein kurzer Abriss über die verschiedenen Konzepte und die Konvergenz interdisziplinärer Forschung vermittelt, die schliesslich zur Definition und Identifikation der hypothalamischen "Releasing factors" und "Release-inhibiting factors" geführt haben. Schliesslich wird eine Klassifikation der neuroendokrinen Systeme vorgeschlagen.

Shortly before his untimely death Geoffrey W. HARRIS (1971) delivered a most remarkable lecture on "Humors and Hormones" in which the evolution of thoughts and facts leading to the identification by Guillemin (see BURGUS et al., 1969) and by SCHALLY et al. (1969) of the "Releasing Factors" or "Releasing Hormones" were clearly outlined. Fig. 1 gives a survey of the many converging multidisciplinary approaches that were necessary before the concept of "Releasing Factors" controlling the glandular activity of the pituitary could be accepted.

The first notion that the hypothalamus governs the activity of the pituitary gland arose from clinical observations by Parisian and Viennese Physicians at the end of the 19th century. Experimentalists then began to explore the hypothalamus, its inputs and stimulatory effects

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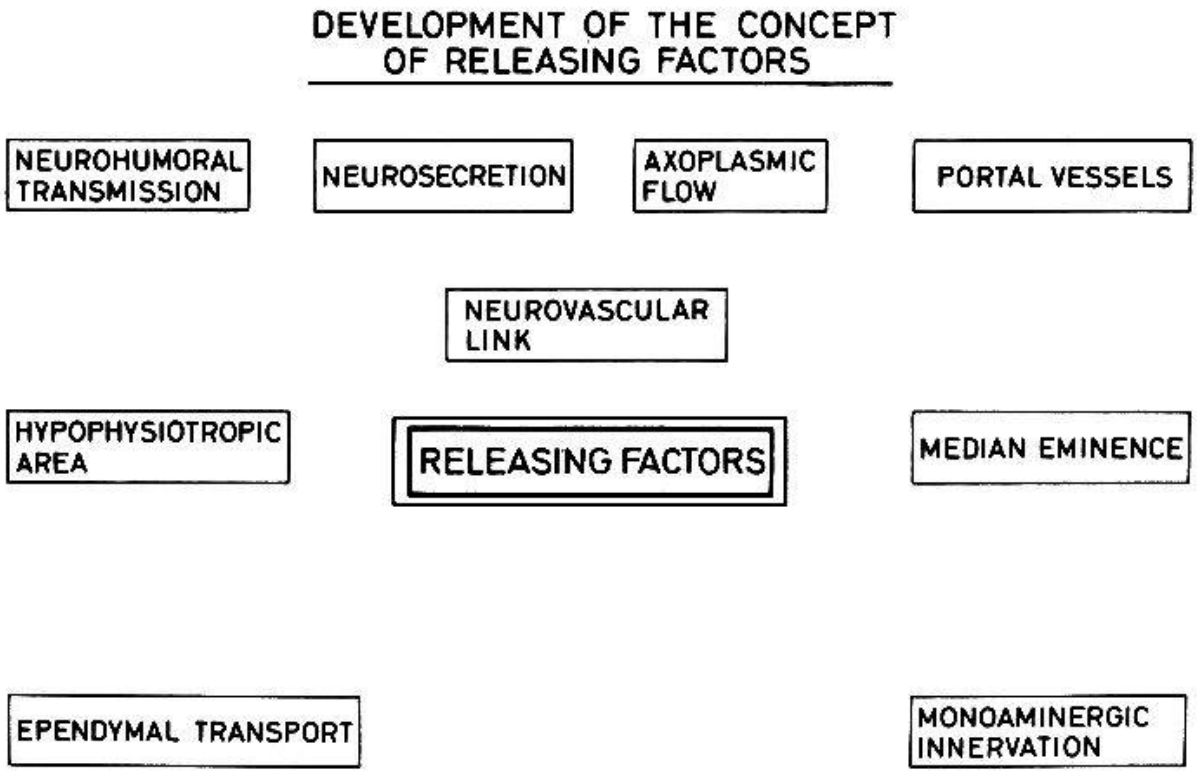

Fig. 1. Development of the concept of hypothalamic releasing factors.

and as a consequence the powerful control area of vegetative and endocrine regulations was successively uncovered (W.R. HESS, 1949). HARRIS (1937) was one of the first to establish the triggering function of a circumscribed area of the hypothalamus by eliciting ovulation experimentally in the unanesthetized rabbit with implanted electrodes. However, he soon realized that the conventional reflex model was not applicable to pituitary control since morphological and physiological evidence of an efferent nerve supply to the adenohypophysis was totally lacking (see HARRIS "Hypothalamic control of the pituitary gland", 1955).

The neurovascular link

The solution of this problem came with three groups of new findings: 1. the discovery of the neurosecretory function of specific hypothalamic neurons, 2. the demonstration of the pituitary "portal vessels", and 3. the functional grafting of the pituitary gland under the pituitary stalk (HARRIS and JACOBSOHN, 1952).

Secretory activity of hypothalamic nerve cells had been heralded by Ernst and Berta SCHARRER since 1928 (see also their reviews in 1965 and 1969). Yet, convincing evidence was provided only in 1949 when Bargmann succeeded to demonstrate the secretory pathway from

the supraoptic and paraventricular nuclei to the neurohypophysis by means of Gomori's chromalum hematoxylin stain (BARGMANN and SCHARRER, 1951). This new insight revolutionized our knowledge on the neurohypophysis which could no longer be considered as endocrine gland per se; it became evident that central neurons are not only electrical but also secretory units. This point of view received strong support by the rapidly accumulating evidence on the chemical nature of synaptic transmission (ELLIOTT, 1905; DALE et al., 1936; LOEWI, 1921) and by the striking observations on the mechanism of cytoplasmic transport along the axon (WEISS and HISCOE, 1948). Chemical identification of the neurohypophyseal hormones by DU VIGNEAUD (1956) as nonapeptides (vasopressin and ocytocin) and the demonstration of ultrastructural correlates of these substances along the hypothalamic neurosecretory pathway in terms of characteristic storage and release granules (PALAY, 1957; BARGMANN, 1966) led finally to the term "Peptidergic neuron" (BARGMANN et al., 1967).

The "portal vessels" were described by POPA and FIELDING (1930) to form a vascular link between pituitary gland and hypothalamus. However, GREEN and HARRIS (1949) demonstrated by directly observing the hemodynamics of this system an "afferent" plexus in the median eminence of the hypothalamus and an "efferent" counterpart in the adenohypophysis thus reversing the concept of the original observers. TÖRÖK's subsequent work (1956) indicated that vascular relationship and orientation of blood flow in the pituitary stalk may be more complex than expected (DUVERNOY, 1972) and it seems likely from recent work that microcirculation studies may soon come up with new and unexpected information on the complexity of this vascular bed, thus partly vindicating the early assumptions of hypothalamopetal flow.

Of decisive value were the transplantation experiments carried out by HARRIS and JACOBSOHN (1952). These authors proved that hypophysical function by transplanting pituitary glands from newborn animals into the region of the sella turcica, i.e. the subarachnoid space below, where regeneration of portal vessels was verified histologically. In contrast, control grafts remote from the hypothalamus survive but maintain only fragmentary endocrine activity.

From these lines of approach it was relatively easy to postulate secretory agents mediating the triggering signals from hypothalamic centers to the glandular cells of the pars distalis of the pituitary. The term "releasing factors" seems to have been first used by SAFFRAN and SCHALLY (1955). Yet, the analogy (Fig. 2) between the hypothalamic neurohypophyseal and the hypothalamo-infundibular units was not immediately evident. First of all, the

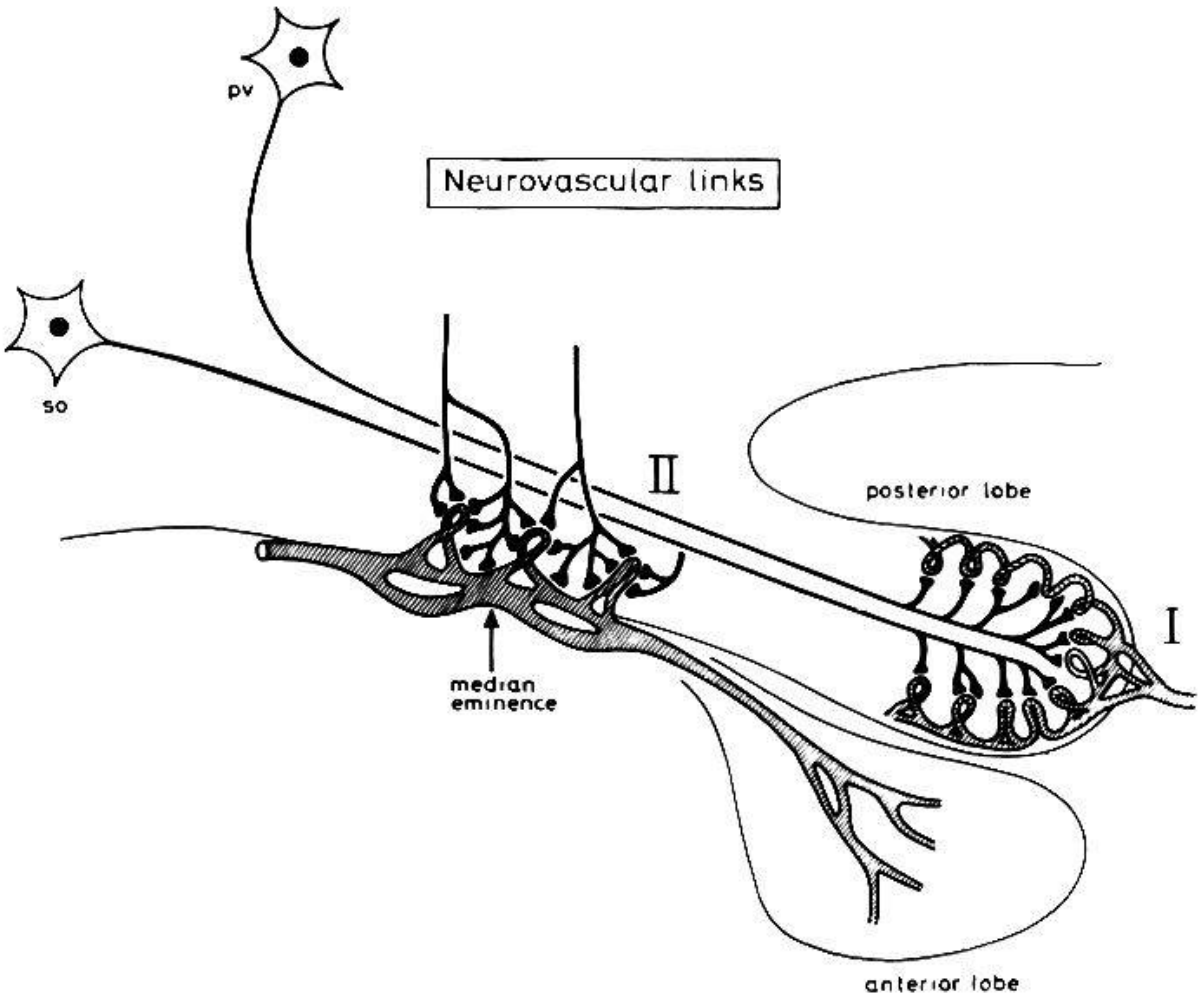

Fig. 2. Comparison between two types of neurovascular links. Type I represents the classical hypothalamo-neurohypophysial pathway, mainly disclosed by Bargmann and Scharrer. so = Neurosecretory neuron of the supraoptic nucleus, pv = Neurosecretory neuron of the paraventricular nucleus. Type II represents the hypothalamo-infundibular system which involves the "releasing factors" and the portal vessels whose primary plexus is located in the median eminence and whose target is the anterior lobe. (Redrawn from Halász, 1972).

perikarya and their axons producing and transporting the "releasing factors" respectively turned out to be Gomori-negative, and secondly the complex neurohemal zone of the median eminence (GREEN, 1951) required laborious efforts by electronmicroscopists (KOBAYASHI et al., 1970) before its functional equivalence with the palisades of the posterior lobe could be established.

The crucial question with respect to the location of the putative "peptidergic neurons" remains unsolved. Their general topography had been delineated by HALASZ and his group in collaboration with SZENTAGOTHAI et al. (1968). These authors (HALASZ, 1969) used the method of de-afferentiation or minimal tissue-island preparation by circumsecting hypothalamic areas necessary for the maintenance of pituitary functions with a fine knife.

Their results were essentially consistent with earlier lesion work (see SAWYER, 1975) and confirmed that the "hypophysiotropic" zone of the hypothalamus included the arcuate nucleus and immediately surrounding cell groups of the tuberal region. However, all these techniques failed to provide direct evidence on the identification of neurosecretory cells, and more parsimonious interpretations referred their data to the neurohemal complex including the terminal network of neurosecretory endings and their contacts with the portal capillary loops (see Fig. 2). Thus, the final evidence is still wanting today and we are hoping for the information to be delivered at the occasion of this symposium. The solution can be expected to come from cytoimmunological marker studies, a very efficient approach to the identification of peptidergic neurons (HÖKFELT) or from micro-biochemical investigations (PALKOVITS, this volume).

Three types of neuroendocrine systems

Since the analogy of the two neurosecretory systems has proved to be so fruitful for the development of the "Releasing factor" concept I would like to briefly consider the classification of neuroendocrine systems that can be derived from present data (Fig. 3). The classical system, called first-order, consists of the supraoptic and paraventricular neurosecretory units and the neurohypophyseal neurovascular link to the various target organs (uterus, kidney, mammary gland, vasomotor system). According to very recent information it seems not inconceivable that these hormones may have an additional target organ, i.e. the brain itself (DE WIED et al., 1976) and perhaps the adenohypophysis (ANTUNES et al., 1977). The second-order system involves the intermediate lobe whose active principale in the mammalian seems to play a more important role than anticipated. Unfortunately, the neurosecretory units concerned and the neurovascular linkage are still ill defined. Nevertheless, this system is clearly different because the presence of an additional endocrine cell in the intermediate lobe contrasts with the lack of a second endocrine activity in the first-order posterior lobe system. Finally, the third-order system involves the adenohypophysis as a second stage and requires a third endocrine cell, situated in the periphery, before the final message reaches the target organ. It should be mentioned, however, that the adenohypophyseal system includes second-order systems as well since the growth hormone affects the target organ without an additional link.

The basic element common to all three systems is represented by the neurosecretory control unit which is localized in the hypothalamus or in the adjacent forebrain, and which produces a releasing or release-inhibiting neuropeptide.

NEUROENDOCRINE SYSTEMS

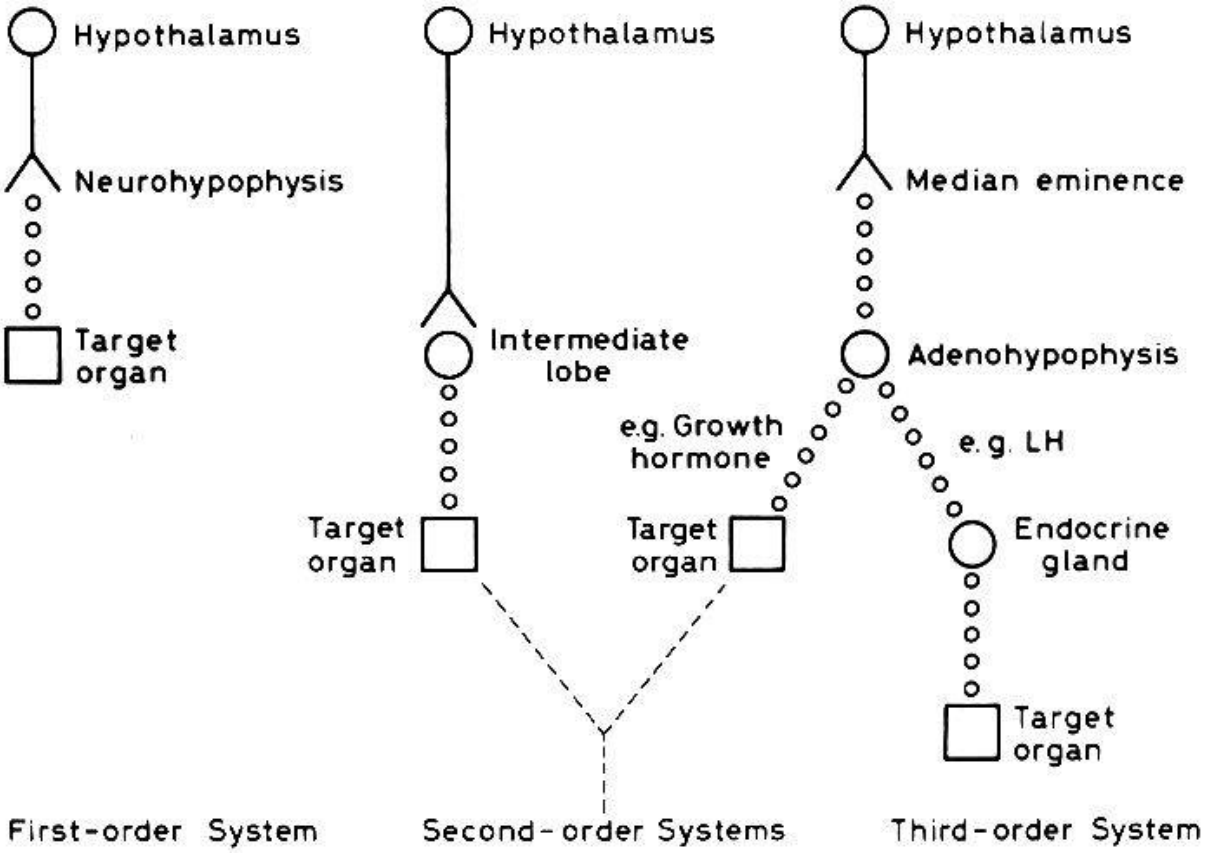

Fig. 3. Classification of neuroendocrine systems. Explanation see text. The third-order system reflects the situation in mammals, since in lower vertebrates the adenohypophysis may be innervated directly by neurosecretory cells.

Complementary mechanisms

The diagram in Fig. 1 includes two additional concepts which may represent steps in the further development in neuroendocrine control theory. One concerns the role of the cerebrospinal fluid and the ependymal lining of the brain ventricles, especially that of the infundibular recess. The findings of several groups of investigators (HELLER et al., 1968; KNIGGE et al., 1975; KNOWLES, 1974; OKSCHE et al., 1974; WITTKNOWSKI, 1968) suggest that the neuropeptides may be present in the ventricles and that receptor and/or transport functions of specialized ependymal cells may exert an influence on the secretion of releasing factors (Fig. 4). Some authors (DE WIED et al., 1976) extend this view by attributing an even more widespread role of neuropeptides in the CNS (learning processes, memory consolidation). The second concept seems to rest on far more solid foundations: the aminergic innervation interacting with the neurosecretory cells at various levels of hypo-

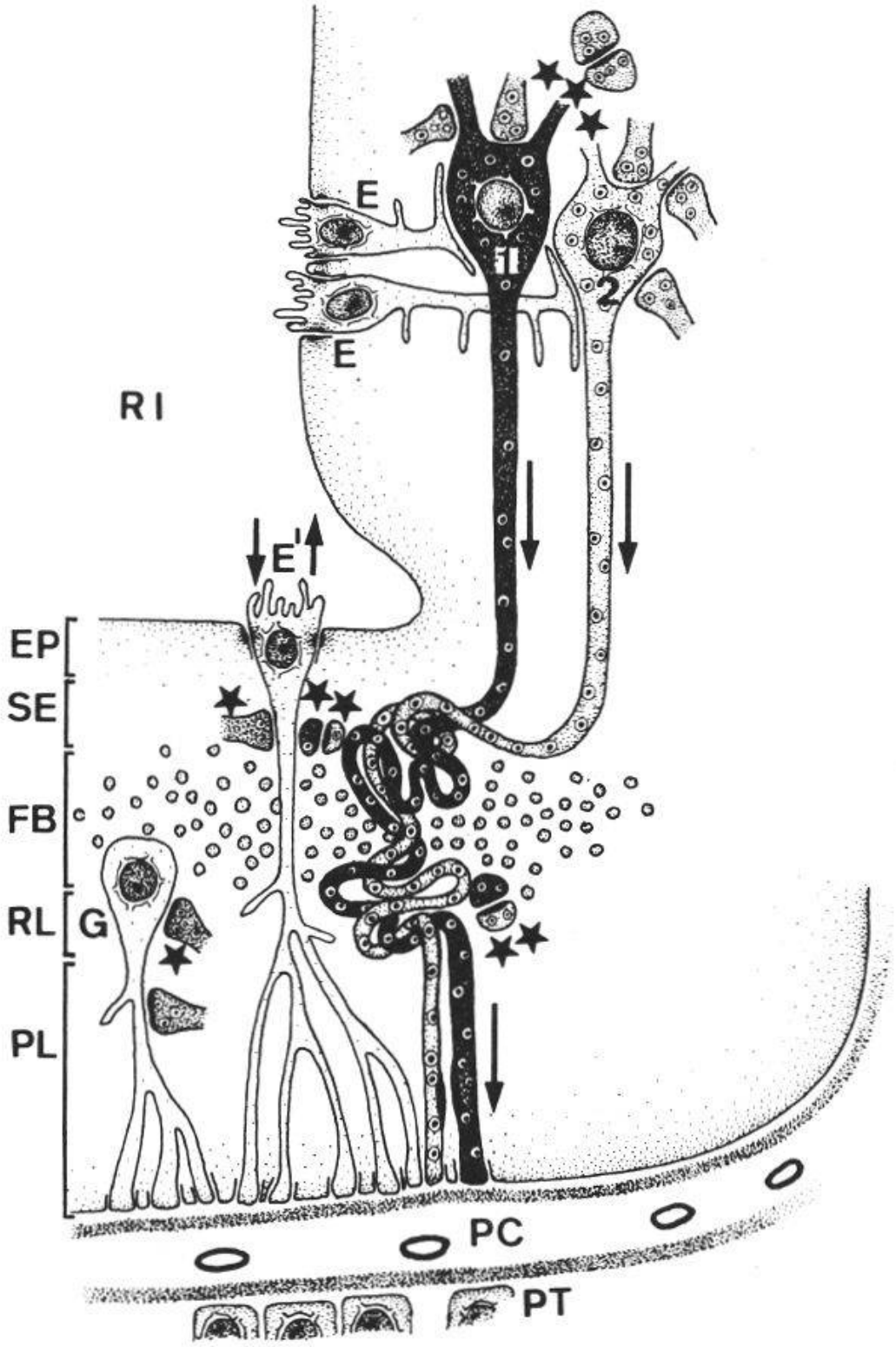

Fig. 4. Hypothetical diagram of the interaction (asterisks) between hypothetical neurosecretory cells and ependyma/CSF system and with aminergic innervation. 1 = aminergic and 2 = peptidergic cell projecting to the palisade layer (PL) of the median eminence. At the surface of the infundibular recess (RI) the possible direction of uptake and/or release of substances in the ependymal cells (E) is indicated by arrows. EP, SE, FB, RL represent the complex structure of the median eminence (from OKSCHE et al., 1973, Fig. 1, Springer-Verlag, Berlin, Heidelberg, New York).

thalamic integration. This innervation can be directly visualized (FUXE, 1964) in the median eminence (Fig. 4) and its origin in the region of the arcuate nucleus, in the ventral thalamus and the reticular formation is firmly established (BJÖRKLUND et al., 1974; FUXE and HÖKFELT, 1969; LICHTENSTEIGER, 1970; LICHTENSTEIGER and LANGEMANN, 1966). Its functional significance was initially sought in the realm of the releasing function itself (SAWYER et al., 1949). Several lines of evidence make it look more likely that these innervation systems (catecholamines, serotonin) encroach directly the releasing cells and thereby enhance or inhibit the release of neuropeptides. Monoamines may, however, be released from non-synaptic boutons and reach the portal vessels thereby directly affecting the glandular cells of the adenohypophysis.

Acknowledgment

The classification of endocrine systems (Fig. 3) was critically improved by Prof. W. Lichtensteiger, Zürich.

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