MESSENGER SUBSTANCES OF NEURONS AND PARANEURONS: THEIR CHEMICAL NATURE AND THE ROUTES AND RANGES OF THEIR TRANSPORT TO TARGETS

TSUNEO FUJITA

Department of Anatomy, Niigata University School of Medicine, Asahimachi, Niigata 951, Japan

REVIEW

Neurons and paraneurons (peptide/amine producing endocrine and sensory cells) share cell-biological features and chemistry of secretions. The bioactive substances or chemical messengers secreted by neurons and paraneurons (peptides, amines, acetylcholine, ATP, etc.) are conveyed to their targets which may be opposed only several nanometers apart or may be located at more or less remote sites in the body. The modes and ranges of the transport of different messengers from different neurons and paraneurons are reviewed. In order to visualize the gradational ranges of messenger transport, the following terms were defined: synaptocrinia, paracrinia, microhemocrinia (pericrinia), mesohemocrinia (mesocrinia) and macrohemocrinia (telecrinia). Transmitters and hormones are thus continuous to each other both in their chemical nature and in the routes and ranges of their transport to the targets. This review further analyses the implications of the concept of internal secretion (endocrinia). The classical concept of endocrinia seems unable to account for the endocrine-exocrine partition of secretions ('leakage' of hormones into exocrine lumen and that of exocrine secretions into blood circulation) of which the mechanism remains to be elucidated in future studies.

HISTORICAL BACKGROUND

Hormones and Transmitters

Until several years ago, it had been generally yet vaguely understood that the chemical messengers produced and released (in a word, secreted) by nerve cells or neurons are represented by transmitters, and those secreted by endocrine cells are hormones. Transmitters should traverse only a very small distance (10-100 nm) of an intercellular space to act upon a juxtaposed target cell (15), whereas hormones are usually transferred by the circulatory system to remote targets (6). An obvious contradiction to this categorization was the phenomenon that 'neurohormones,' such as vasopressin and oxytocin, are produced by 'neurosecretory neurons' and released into the circulation to be sent to remote targets (5). This

contradiction, however, seems to have caused few substantial disputes on the nature of transmitters and hormones, until numerous peptide-containing or 'peptidergic' neurons were recently discovered. The peptides contained in these neurons, somatostatin, substance P, vasoactive intestinal peptide (VIP), cholecystikinin (CCK), etc., obviously corresponded to hormones produced by endocrine cells on one hand, and on the other, their 'synaptic vesicles' undistinguishably resembled endocrine secretory granules.

Recent studies of gut hormones came to suggest that they may be only partly transferred to their remote targets by the circulation and mainly exert their actions upon vicinal targets in the intestinal wall, including muscle cells, neurons and secretory cells. In the 1970's attention was gradually focused upon the role of gut hormones

as locally acting messengers rather than as hormones in the classical sense (36–38, 93). Actually it appeared that many of the peptidic and aminic hormones and their candidates found in the gut were so quickly inactivated after entering the circulation that they could exert very slight effects on remote organs, if any at all (90). Diabetologists, on the other hand, came to conceive the local or intra-insular actions of glucagon and somatostatin on the insulin secreting activities of B cells (28, 56, 91).

Feyrter's Paracrinia

In 1953, Feyrter (24), a pathologist in Vienna proposed the term, 'Parakrinie' (paracrinia) to indicate his hypothesis that 'helle Zellen' (clear cells) which he found disseminated in the epithelia of the digestive tract and airway ('diffuse endokrine epitheliale Organe') (20–23), might send their secretions to vicinally located targets. The clear cells of Feyrter correspond to the endocrine cells which at present are known to be the sources of a large variety of peptidic and aminic messengers. Some recent researchers (36, 59, 90, 93) noticed the usefulness of the Feyrter's concept of paracrinia in present-day disciplines, especially in gastroenteric endocrinology. The term and concept of paracrinia have thus served the recognition of the short range transfer of hormonal messengers.

Although the term paracrinia has become widely accepted, neither Feyrter nor recent advocates of his concept have defined the term precisely. Apparently they have not been interested in determining the range and route of paracrine messengers. Feyrter himself seems to have used the term quite vaguely. On page 70 of his paper written in 1962, Feyrter (25) notes that paracrinia is a 'humorale Beeinflussung anliegender Zellen und Gewebe' (humoral influence of closely opposed cells and tissues) and includes, besides the hormone transfer by diffusion, also that by such blood vessels as from the islet of Langerhans to the exocrine pancreas and from the adrenal cortex to medulla.

In a later section of this paper, we will define the term, 'paracrinia' more precisely than previously defined. Without such a definition, the science of chemical messengers may encounter difficulty in advancing on a sound theoretical and experimental basis.

Neurons and Endocrine Cells Are Inseparable

It has long been believed that neurons are special,

elite cells which can and should be precisely distinguished from other cells by their structure, function, metabolism and origin. However, each of these features of neurons was demonstrated, in recent cell-biological studies, to be shared by many non-neuronal cells. Action potential-like electric reaction was found to occur in glucose-stimulated B cells of the pancreas (14, 80) and several other endocrine cells (3, 9, 10, 113). The monoamine producing ability was demonstrated by Pearse and associates to be shared by many neurons and endocrine cells, which Pearse categorized as APUD series (87–89). 'Neurosecretory-like' and/or 'synaptic vesicle-like' granules correspond in structure to the granules of peptide/amine-producing endocrine cells and sensory cells. Based on this knowledge of the continuity of the endocrine cells and sensory cells to the neurons, these non-neuronal but neuron-like cells have been designated as paraneurons (30, 31, 38).

The endocrine variation of neurons may be represented by classical neurosecretory neurons in the hypothalamo-hypophyseal system and other peptidergic neurons which are especially gathered densely in the hypothalamus but distributed widely in the central and peripheral nervous systems (101). Actually it has been criticized that the paraneuron family should include the neurosecretory cells (47). We conceive that it is more reasonable and might cause less confusion to scientists to leave the classical neurosecretory cells in the category of neurons, although they are located in cell-biological characters between neurons and paraneurons. As noted by B. Scharrer (100) already in 1969, the boundary between the 'classical' neurosecretory neurons and 'ordinary' neurons has become increasingly vague. A variety of 'peptidergic' neurons (101) demonstrated in different parts of the body and at different levels of evolution of animals accelerated to remove the boundary (72).

The cerebrospinal fluid-contacting neurons seem to represent another category of cells located at the boundary of neurons and paraneurons and retaining primitive features of neurons (73, 119). As their homologues, pinealocytes in the pineal body and visual cells in the retina (118, 120) represent typical endocrine and sensory paraneurons, respectively.

Olfactory cells have long been believed to be typical neurons. As, however, evidence supports their continuous renewal from the nasal epithelium (43), through an immature type of basal-granulated cells (125), they are better categorized into the paraneuron (7, 38).

Numerous other instances can be counted which indicate a non-neuronal nature of neurons or neuronal nature of endocrine or sensory cells. There are different intermediate forms between neurons and paraneurons and no clear boundary can be drawn between them. This continuity in cellular elements of the nervous and endocrine systems obviously represents one of the pair of wheels together with the continuity in chemistry of messenger substances produced by both systems, which will now be dealt with.

SECRETIONS OF NEURONS AND PARANEURONS

Secretions or Granule Contents of Neurons and Paraneurons

Advances in chemical and immunohistochemical studies have made it clear that neurons in the central and peripheral nervous system share numerous bioactive peptides with the endocrine and sensory paraneurons, especially in the gut and pancreas (Table 1). The term, 'brain-gut peptides' has thus become useful.

Moreover, substances, other than peptides contained in the secretory granules (including the synaptic vesicles) are believed to be common to neurons and paraneurons (30, 32, 38). The best known elements comprise bioactive monoamines such as noradrenalin, adrenalin, dopamine, serotonin (5HT) and occasionally histamine. These amines may often serve as potent transmitters or hormones, although only a part of

neurons and paraneurons contain them, at least in such a condensation as detectable by histochemistry.

More constant elements in the secretory granules of neurons and paraneurons are ATP and other adenine nucleotides, large acidic carrier proteins of glucoproteic nature as well as a high concentration of Ca^{2+} (Table 2) (30, 32, 38).

Today's knowledge on the chemical contents of neuronal and paraneuronal granules are based mainly on the advanced investigations of the chromaffin granules of the adrenal medulla. These studies recently revealed that dopamine- β -hydroxylase (DBH), which is an important enzyme in chromaffin cells, is a kind of glucoproteins closely resembling, in molecular structure, the chromogranin A which has long been known as an acidic carrier protein in the chromaffin granules (124). Chromaffin granules have been shown to contain also such strongly acidic mucopolysaccharides like haparan sulfide and chondroitin sulfate (77, 124). Highly negatively charged mucopolysaccharide resembling heparin has been demonstrated in cholinergic synaptic vesicles, representing the major constituent of vesiculin (108, 122). All these weakly and strongly acidic polysaccharides and glucoproteins are believed to cause the metachromatic reaction of granules of neurons and paraneurons, after removal of the conjugated basic substances by gentle hydrolysis of tissue sections with HCl (107). These metachromatic substances have

Table 1 *Representative Bioactive Peptides in Neurons and Paraneurons ('Brain-Gut Peptides') Based on the Knowledge Gathered in Human and Animals above Amphibia*

Known only in NEURONS	Oxytocin, Vasopressin LHRH, GHRH, CRH
Known to occur both in NEURONS and PARANEURONS	TRH Neurotensin ACTH, MSH, Endorphins, Enkephalins Calcitonin Somatostatin Substance P GIP (Gastric Inhibitory Peptide) VIP (Vasoactive Intestinal Peptide), PHI Glucagon/Glicentin, Insulin CCK (Cholecystokinin)/Gastrin GRP (Gastrin Releasing Peptide)/Bombesin PP (Pancreatic Peptide), NPY, PYY Motilin
Known only in PARANEURONS	Secretion PTH (Parathormone)

Table 2 *Secretions (Granule Contents) of Neurons and Paraneurons*

	Adrenal chromaffin granules	Other endocrine and 'peptidergic' granules	Small synaptic vesicles
Polypeptides-peptides	+; <i>e.g.</i> , pro-opioid-enkephalins	+; <i>e.g.</i> , proinsulin-insulin Somatostatin 28-14	- ?
Monoamines or acetylcholine	+	+ (may be absent)	+
ATP and other nucleotides	+	+	+
Glucoproteins and mucopolysaccharides	+; chromogranins, DBH, mucopolysaccharides	+; <i>e.g.</i> , neurophysins, acidic glucoproteins	+
Lipids	+	+	?
Ca ²⁺	+	+	+

been demonstrated in a variety of neurons and paraneurons, as far as they store a certain amount of secretory granules (34, 40, 63), whereas they are not recognized in other granule containing cells like those of exocrine glands. They must be important granule components of neurons and paraneurons combining with basic substances including amines and peptides.

The granules of neurons and paraneurons are believed to contain also trypsin-like enzymes involved in the processing of polypeptidic pre-hormones to final fragments.

The neuronal and paraneuronal granules contain considerable amounts of lipids but the chemical and cytochemical studies are not advanced (124). It seems possible that lipids are incorporated in glucoproteins to form glucolipoproteins. The somewhat osmophilic nature of the granules of neurons and paraneurons under the light and electron microscopes seems primarily due to the contents of lipids in the granules.

Although the chemical components of secretory granules in different neurons and paraneurons have not been demonstrated as precisely as in the chromaffin granules, more and more data are being accumulated which suggest that every neuron and paraneuron might contain essentially the same combination of substances in their granule contents (30, 33, 124) (Table 2).

A possible exception seems to be represented by small synaptic vesicles in so-called cholinergic and adrenergic types of neurons. Recent chemical studies suggest that they contain adenine nucleotides but neither peptides nor glucoproteins (60) (Table 2). These vesicles, differing from the 'large cored vesicles' (endocrine-like granules) usually mingling within them, are probably formed at the terminal site of neurons and their contents consist of reabsorbed secretions of the neuron (60, 61).

Dale's Law Must Be Revised

Under the Dale's law, it has long been believed that one neuron produces and releases one transmitter. The theory in endocrinology corresponding to the law of Dale reads that one cell secretes one hormone (one cell-one hormone theory). According to the recent knowledge introduced above, it is now apparent that these theories must be largely revised.

The first reason for this revision is that it is not a transmitter or hormone which corresponds to a neuron or an endocrine cell, but it is a set of substances including a transmitter or hormone. As detailed above, this set consists of peptides, amines or acetylcholine, ATP, glucoproteins and mucopolysaccharides, Ca²⁺, *etc.* (30-32, 124). According to the cells, the bioactive substance comprises a peptide, amine or acetylcholine. However, this means that the main bioactive agent is it. Different components of the substance set may possess bioactivity simultaneously.

Recent immunohistochemical studies indicate that 'adrenergic' or 'cholinergic' neurons may simultaneously be peptidergic. Somatostatin (55) or opioid peptides (123) have been demonstrated to be contained in mammalian peripheral noradrenergic nerves, whereas VIP in intestinal cholinergic nerves (76, 102). It must be newly investigated as to whether, for instance, VIP contained in the nerve concerned may be predominant or subsidiary to the simultaneously contained acetylcholine in function. It is also a problem to be settled as to whether peptides are stored in 'large cored vesicles' (endocrine-like granules) in the nerves, separately from amines and acetylcholine which are contained in small synaptic vesicles.

The endocrine-like paraneurons in the bron-

Fig. 1 Representative members forming the secretory complexes in the granules of neurons and paraneurons (left). The members are separated when released from the cell by exocytosis (right).

chial epithelium contain simultaneously serotonin and gastrin releasing peptide (GRP) (110). The serotonin containing EC cells in the gut are believed to contain a peptide hormone, which has not yet been identified (62).

Not only peptidic and aminic substances, but also ATP and other adenine nucleotides may exert their activities upon certain targets. It is not only the Burnstock's 'purinergic' neuron (12) that releases adenine nucleotides but every neuron and paraneuron secretes them and therefore can be said to be more or less purinergic (32). Studies have not advanced concerning the possible functions of glucoproteins released from neurons and paraneurons, except for some unconfirmed data on the activities of neurophysins (97, 99, 115).

The second reason for the revision of the Dale's law and the one cell-one hormone theory is that we may have increasing instances of two or more peptide hormones occurring in one and the same neuron or paraneuron. There are two categories in this phenomenon. One is that the apparently different peptides are really fragments produced by the procession of a single large precursor molecule. As a typical example, MSH, ACTH, β -endorphin, etc. in the same pituitary endocrine cells are the fragments of a large ACTH- β -lipotropin precursor (82). In the second category of peptide coexistence, we could, at least at present, obtain some evidence for a common precursor. Simultaneous occurrence of somatostatin and calcitonin in the parafollicular cell (117), gastrin and enkephalin

in gastric G cell (65, 69, 94) and glucagon and GIP (2, 106), cholecystikinin (45) and/or α -endorphin (46) seems to represent the instances in this category of peptide coexistence. In neurons, on the other hand, coexistence of two peptides, such as oxytocin and cholecystikinin in rat and bovine hypothalamus (116), enkephalins together with oxytocin and vasopressin in rat neurohypophysis (78), somatostatin and avian pancreatic peptide (APP) in rat and human cerebral cortex (121), cholecystikinin and substance P in rat dorsed root ganglia (13) and mesencephalic neurons (105) occurs.

At any rate, it seems reasonable to postulate that the coexistence of the same and different categories of substances in the granule contents of neurons and paraneurons might be accounted for by the purposefulness of the simultaneous release of these substances from the same cell by the same stimulus. In other words, it is presumed that the set substances released from the same neuron or paraneuron will exert their actions synergetically in a broad sense, although only little concrete evidence for this postulation is available at present.

Release of Secretions

Electron microscope studies as well as physiological experiments mostly support the view that the contents of their secretory granules (including synaptic vesicles) are extruded, at least in physiological states, by the Ω -shaped opening of the granule membrane to the plasma membrane of

Table 3 *Gradations in the Routes and Ranges of Chemical Messengers*

	Route	Order of range	Messenger
1. Synaptocrinia	Intercellular diffusion	10–100 nm	Synaptic messenger
2. Paracrinia	Intercellular diffusion	μm	Parahormone
3. Microhemocrinia = Pericrinia	Microcirculations	μm –mm	Perihormone
4. Mesohemocrinia	Intervisceral portal vessel	cm	Mesohormone
5. Macrohemocrinia = Telecrinia	General circulation	cm–m	Telehormone

the cell. This mechanism of granule release, called exocytosis, means that the set of the secretory substances above mentioned are liberated at the same time, and probably in a fairly constant quantitative ratio, from their membrane package to the extracellular space (30, 38, 61, 124).

When a neuron or paraneuron is adequately stimulated, the stimulus-secretion coupling of the cell is triggered and the exocytotic granule release results. By this mechanism, the secretions of the cell can be released *in quanta*, i.e., package after package, according to the intensity of the stimulus (38, 61) (Fig. 1).

ROUTES AND RANGES OF MESSENGERS

Discussions in the previous sections provide us with the basis upon which we can treat the secretions of neurons and endocrine cells in common. From this basis, we will now turn to the routes and ranges of bioactive missiles released from neurons and paraneurons.

Missiles with the shortest range are represented by neurotransmitters which travel only 7–40 nm through the synaptic cleft to reach their target. Intercontinental ballistic missiles are hormones conveyed by the general circulation through the body reaching remote targets. Every gradation exists between these extremities. A large variety of intermediate and medium range missiles can be found in different parts of the body and in different animals. The mode of the transport of neuronal and paraneuronal messengers will be classified below according to their routes and ranges (Table 3, Fig. 2).

Synaptocrinia

When a messenger substance released from a cell runs by diffusion through an intercellular slit to the surface of a juxtaposed target cell, this mode of messenger transfer may be called *synaptocrinia*.

Typically, synaptocrinia is seen in neurotransmitters released by neurons into synapses. The synaptic cleft usually is only 10–30 nm wide, but a basement membrane may be intercalated, widening the cleft to about 60 nm, as in the case of neuromuscular junctions (15).

Sensory paraneurons, such as olfactory, gustatory and bronchial neuroepithelial cells as well as Merkel cells in the skin, give their messengers to the juxtaposed afferent nerves by synaptocrinia.

Endocrine paraneurons may occasionally exhibit morphologic features suggesting synaptocrinia. Somatostatin producing D cells in the fundic region of gastric mucosa may extend a slender process to contact with a parietal cell, leaving only a synapse-like slit. The tip of the process usually is swollen and filled with somatostatin-immunoreactive granules (66–68). This feature of D cells has been correlated to the known inhibitory effect of somatostatin upon acid secretion of the parietal cells (66–68). It is worthwhile to notice, however, that this interpretation could not be free of contradiction, as the parietal cells touched by a D cell process are limited to only a few percent of the whole parietal cells. Even if one admits a possibility that D cells might busily move their processes to touch different parietal cells, only a small part of parietal cells may be under the synaptocrine control of the D cells. It seems reasonable to assume that somatostatin released by D cells affects the parietal cells partly by synaptocrinia and rather mainly by paracrinia, diffusion of a longer range. The same seems to hold true in the case of somatostatin cells extending a process in contact with gastrin producing G cells in the rat pyloric antrum (1). Direct contact of elongated processes of somatostatin producing D cells to exocrine cells in avian proventriculus (57) has been demonstrated. Similar synaptocrine figures of EC and some other cells have been also recorded (67).

It is presumed that synaptocrine as well as

Fig. 2 Gradation in the ranges of messenger transport. Note that neurons and paraneurons are equal with regard to their relation to the target cell (T) and blood capillary (B).

paracrine control or modulation of neighbor cells may be exerted also by other paraneurons, especially at those sites where different types of paraneurons are gathered to form an endocrine organ. Gap junctions may serve the synchronous excitation of adjacent cells (86) but have nothing to do with the intercellular communication by chemical messengers, as these must be transferred, not through the plasma membrane channels, but through an intercellular space to exert their actions upon the receptors on the free surface of the target cell. Recent experiment supports that extracellular but not intracellular application of peptide hormones activates the target cell (92).

Paracrinia

As noted above, the concept and term of paracrinia originated by Feyrter has become popular

in recent studies, but nobody seems to intend to define the concept precisely. Vaguely, it seems to be understood as indicating transfer of a chemical messenger through intercellular spaces to vicinal targets, but its routes and ranges differ conspicuously among authors. What we call synaptocrinia, *e.g.*, D cell's secretion upon its associated target cell (*vide supra*), has been called paracrinia by Larsson (67, 68). Transfer of islet hormones to the exocrine pancreas by microcirculation has also been included in paracrinia by Feyrter (25).

In this paper, it is proposed to use the term paracrinia in a more restricted range: Paracrinia is transfer of a chemical messenger to a vicinal target by *intercellular diffusion*.

In neurons a 'synapse à distance' has long been known, in which the target is located some 200 or even 400 nm apart from the neuronal terminal. Some smooth muscle cells, for instance, have

been claimed to receive synapses à distance (74). This category of 'synapse' falls in the range of paracrinia (Fig. 2). Different endocrine paraneurons are suspected to be under a paracrine control or modulation of nerves. Gut endocrine cells, especially G cells (71) and EC cells (37), may be found to approach nerve terminals, leaving a 200–300 nm distance. As if to correspond to this finding, vagal effects upon gastrin releasing G cells (8, 44, 79) and upon serotonin releasing EC cells (114) have been documented.

Microhemocrinia or Pericrinia

In this category of messenger transport, a chemical messenger enters blood capillaries and, after being carried by them for a certain distance may emerge from them to affect extravascularly located targets (Fig. 3).

In pancreatic islets, the possibility has been discussed that glucagon from A cells and somatostatin from D cells might be transferred by microcirculation to B cells whose insulin secretion is stimulated by glucagon and suppressed by somatostatin. This view is supported by the morphological findings that blood capillaries in islet in different animals are so designed that blood flows from the A and D cell areas to the B cell area (29, 39, 41).

Similar instances of hormone transportation

by microcirculation may possibly be found in different endocrine glands, but studies on this viewpoint are very few if any. The characteristic position of parafollicular cells disseminated in the thyroid follicles, for instance, must be considered with regard to the possible actions of parafollicular cell secretions (somatostatin, calcitonin and monoamines) upon the follicular cells either by paracrinia or by microhemocrinia, or by both.

In the villi and crypts of the intestine, blood capillaries are extended unusually long along the epithelium in which endocrine cells are dispersed. These capillaries may presumably be involved in the transportation of gut hormones to other parts of the villus or crypt to exert secretory, contractile and possibly also trophic effects upon different elements of these structures. Recent studies suggest that the capillaries in the walls of intestinal crypts, where the endocrine cells are most numerous, send their blood up to the capillaries in the base of the villi (42, 83, 85).

An advanced type of microhemocrinia is the transport of a messenger by small portal vessels. The messenger enters blood capillaries which form the first vascular bed, then is transferred *via* small portal vessels, which usually are also capillaries in histological structure, to a second vascular bed located not so far but at a distinctly different site, either within the same organ or in

Fig. 3 Different routes followed by messenger substances released from a gut endocrine cell. Similar relations may be found also in many other neurons and paraneurons.

Fig. 4 Microcirculation of the mammalian pancreas. Note the insuloacinar portal vessels (P) radiating from the islet of Langerhans (L) to the exocrine capillary bed. A: intralobular artery, V: vein

an adjacent organ (53, 85). The well known instance of this category of microhemocrinia is the hypophyseal portal system conveying hypothalamic neurohormones (releasing and release-inhibiting hormones) to the adenohypophysis.

In the pancreas insuloacinar portal vessels (Fig. 4) convey hormones and neurosubstances issued into the capillaries in the islet to the exocrine pancreas to control its secretory activities (29, 39, 41, 52, 54, 84). Electron microscopic and immunohistochemical observations in some mammals suggest that VIP, acetylcholine, noradrenalin and presumably also dopamine, besides islet cell hormones, are released into the portal vessels and the secretagogous actions of these neurosubstances have been analyzed (35, 39).

In the liver, another example of microhemocrinia may be seen in the periductular portal vessels which originate from the capillary plexus surrounding the hepatic ductules and pour into the lobular sinusoids (81, 85) and presumably convey hormones issued from the endocrine cells in the ductular epithelium. It is an attractive hypothesis that these hormones released from the cells in response to the chemical or

physical information of the flowing bile might exert a kind of feedback control upon the hepatic lobule (31). Substance P has been reported to be contained in endocrine cells in the bile ductules (50, 51) and this peptide is furthermore known to increase the sinusoidal blood flow in the liver (18).

Further possible small portal vessels transporting messenger substances have been and are being searched. Attention has been focused to an antrofundic portal system which might convey gastrin released in the pyloric antrum to the gastric body which contains the HCl secreting parietal cells, the targets of gastrin. This portal system has been postulated because it seems very unpurposeful for gastrin to be transported by the general circulation back to the closely located gastric body (48, 112). Although some experiments pursuing the radioactive tracer injected in the rat antrum supported the existence of the portal system (112), no morphological studies convincingly demonstrating it are available.

An enteropancreatic portal system, which could account for the enteropancreatic and enteroinsular axis (48), was shown not to exist

(98).

Whichever fact or dream might it be, attempts to hypothesise or discover a new microcirculatory route for transport of a given hormone to a vicinal target seem worthwhile and promising.

Mesohemocrinia or Mesocrinia

Transportation of neuronal and paraneuronal messengers by a larger portal system may be called mesohemocrinia, or simply mesocrinia, as it has an intermediate range between the above described small portal systems and the general circulation. In mammals the only representative of the vascular route of this range is the hepatic portal vein. The gastro-enteropancreatic (GEP) neuroendocrine secretions—a large variety of peptidic, aminic and other categories of bioactive substances—are conveyed by this vein to the liver. Here the hormones exert known and unknown effects on hepatocytes, ductular cells and possibly other elements in the liver. The best known among them may be the glycogenolytic and glycogenetic actions by insulin and glucagon, respectively, upon the hepatocytes, as well as secretin's secretagogous effect on the water and bicarbonate release from the bile ductules in the liver (17). The effect of substance P enhancing the sinusoidal blood flow (*vide supra*) must also be taken into account. Furthermore, recent studies indicate that some GEP hormones, especially insulin and glucagon, have trophic effects upon the liver parenchyme (11, 49, 109).

Macrohemocrinia or Telecrinia

This is the classically known endocrinia *via* general circulation. Some messengers have long half lives and circulate many times through the body, whereas others are inactivated or absorbed so quickly that they hardly round the body once. Not only the classical neurohormones vasopressin and oxytocin, but also some new neuropeptides, especially VIP, have been known to be released amply into the circulation after the nerves containing them are stimulated (19). The possible actions of these neurosubstances by micro-, meso- or macrohemocrinia seem an important task of the future study.

Other Routes

Ventriculocrinia Numerous kinds of neuronal peptides and amines have been found to be contained in considerable concentrations in the

cerebrospinal fluid taken from the cerebral ventricles (95, 100). Histological observations are available on the bulbous endings containing peptidergic, adrenergic or cholinergic vesicles and protruding into the ventricular space (100). Beaded axons have been recognized running on the surface of the ependymal lining (103). Moreover, dendrites of liquor contacting neurons, which are numerous in the hypothalamus of lower vertebrates, apparently release their neurosubstances into the third ventricle (*vide infra*) (73, 126).

The messenger substances released into the cerebrospinal fluid are believed to exert a variety of their actions upon different systems in the brain without being hindered by the blood-brain barrier. One can mimic these actions by injecting a known peptide or amine into the human and animal cerebral ventricle.

The term, ventriculocrinia is proposed in this article as referring to the release of any messenger substances into the cerebrospinal fluid. The Latin word 'ventriculus' does not fit the Greek 'crinia', but the same awkward terminology is generally admitted in the case of cerebral ventricle, like 'ventriculography'. In his recent classification of messengers, Epplé (16) calls messenger substances released into the cerebrospinal fluid, 'CSF hormones'.

Lymphocrinia It is possible that some chemical messengers may be transferred by lymphatics, although studies on this problem seem very meager. The thyroid contains a well developed lymphatics in its lobules, which are believed to serve, though to a small part, the transport of thyroid hormones (64, 104). In neuroendocrine tissues, lymphatics seem less important in the transport of the messenger substances, because the lymph capillaries are usually distributed much farther from the mucosal epithelium containing the secretory elements than blood capillaries are.

Lymphocrinia, at any rate, may be included in telecrinia and macrohemocrinia, as the substances which have entered lymphatics must be recovered into the blood circulation in order to reach their targets.

Notes on Terminology Literature indicates that some of the term proposed in this article had already been suggested by previous authors. 'Hämokrinie' was used by Feyrter (25) which is, in contrast to Parakrinie, hormone transfer to remote targets by blood stream. The term 'telecrinia' had been proposed by Leibson (72) in his classification of messengers and their ranges which corresponds in principle to that proposed

Table 4 *Classification of the Modes of Secretion*

EXOCRINIA or External Secretion	
ENDOCRINIA or Internal Secretion in broad sense	
1. Synaptocrinia	
2. Paracrinia	
3. Microhemocrinia (Pericrinia)	} Endocrinia in narrow (classical) sense
4. Mesohemocrinia (Mesocrinia)	
5. Macrohemocrinia (Telecristia)	
6. Ventriculocrinia	
Lymphocrinia, etc.	

in this paper.

Leibson (72) suggests terms of 'parahormones' and 'telehormones' for hormones and neurohormones conveyed by paracrinia and telecristia, respectively. These terms seem very useful and are adopted in this paper (Table 3). Epplé uses also these terms in his recent review (16). It is worthy of note that Karlson (59) recently proposed the term of paramone instead of parahormone. This term sounds not logical because 'mone' has no sense, but this seems not an enough reason to refuse this term as we have long accepted the term pheromone. Messengers transferred by microhemocrinia (microcirculation) may be called perihormones and those by mesohemocrinia (*via* an intervisceral portal vessel), mesohormones (Table 3).

ENDOCRINIA AND EXOCRINIA

Concept of Endocrinia

Confusion is prevailing concerning the definition of internal secretion or endocrinia. The first view is that the 'internal' or 'endo-' should be simply contrasted against the 'external' or 'exo-'. Historically, the direction of secretion was considered at the level of the organ, as to whether the gland is provided with an excretory duct or ducts, or is 'ductless'. However, in the present-day doctrine, the problem should be discussed at the cellular level. Endocrinia must be understood as secretion not towards the apical or luminal pole of the cell but towards the basal or connective tissue side of the cell.

The second view is that endocrinia should be the secretion into the blood circulation. By this route the secreted substances, hormones, should be transferred to remote targets in the body.

Although both views seem faithful interpretations of Claude Bernard's idea of *sécrétion interne*, it is apparent that the second view has more difficulties to coordinate the recent endocrinological findings and concepts. The main

reasons are as follows:

1) Endocrinia in the second sense (macrohemocrinia as designated in this paper) cannot include paracrinia and synaptocrinia, the phenomena which are continuous to and not discriminable from macrohemocrinia.

2) In lower animals without a circulatory system, 'humoral' or 'hormonal' agents are transferred to their targets by paracrinia; if we use the second definition of endocrinia, they must be said to have no endocrine system or activity. Yet it has been recently demonstrated that those agents are common or similar in molecular structure to typical hormones in higher animals including mammals.

In consideration of these contradictions, a reasonable and clear classification of the phenomena of secretion seems to be sought in the first definition of endocrinia. Endocrinia, then, can be simply opposed against 'exocrinia' and includes not only paracrinia but also synaptocrinia (Table 4). This newly proposed concept of endocrinia seems important to smoothly coordinate the new knowledge of the continuity of transmitters and hormones. However, the second classical definition of endocrinia may be worthwhile to be retained as 'endocrinia in its narrow sense'. The new system of secretion is diagrammatically shown in Table 4.

Exocrine and Endocrine Polarity of Cell

In the new system of secretory phenomena the cell polarity is of essential importance, as to whether the secretions are released to the external milieu (or its continuation or modification) or to the internal milieu. This system, theoretically, appears complete and undisputable. In reality, however, there is a problem which might conflict with this system: the possibility has been repeatedly suggested or, at least partly, even evidenced that exocrine glands send a part of their secretions into the circulation and endocrine tis-

sues release a part of their secretions into the lumen or external milieu.

As widely known, small portions of amylase, trypsinogen and other enzymes secreted by the exocrine pancreas enter the blood circulation. Pancreatic hormones, *i.e.*, insulin, glucagon and somastatin have been reported to be included in the pancreatic juice (4, 70, 96). Gastrin is released into the gut lumen in more or less significant amounts (26, 58).

Without morphological or physiological findings convincingly supporting the view, these phenomena have often been explained as 'leakage', *i.e.*, the movement of bioactive agents through the epithelial boundary in a direction reverse to that of the normal secretion. An alternative hypothesis is that exocrine cells might function to release a part of their secretions on the basal or vascular side, whereas endocrine cells might do that on the apical or luminal side. The hypothesis of 'Endokrinie-Exokrinie' proposed by Feyrter (23) in his study of paracrine clear cells or basal-granulated cells are remembered, although the theory has been neglected for long time and especially recent electron microscope studies have given no support to it.

The problem of the polarity of secretion is even more important in neurons. Recent immunohistochemical studies have revealed occurrence of immunoreactive substances (amines and peptides) not only in axons running from the neuronal somata to their targets, but usually also in dendrites to which one had not expected the occurrence of a neurotransmitter or neurohormone. The possibility that the immunoreactive substances might have moved by diffusion during specimen preparation from the soma to the remote ends of dendrites is difficult to support. Together with Llinas (75), it seems reasonable to suggest that neuronal dendrites may transport centrifugally and release neurosubstances, while conducting electrical excitation centripetally. A clear instance of possible dendritic secretion can be found in the cerebrospinal fluid contacting neurons in higher and lower vertebrates. These cells are typical bipolar neurons and immunoreactive substances usually are found not only in their long axons, but also in their drumstick-like dendrite projected to the cerebrospinal fluid (27, 111, 126). The end of the dendrite is swollen by immunoreactive substances filling it. It is likely that the bioactive substances are released here into the cerebrospinal fluid; the fluid is known to contain considerable concentrations of these substances (100, 126).

The above discussion makes the view likely that, in both neurons and paraneurons, a phenomenon to be called 'exocrine-endocrine partition' might possibly be taking place, and morphological and physiological analysis of its mechanism seems of keen importance in future investigation.

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