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Review

The system of cerebrospinal fluid-contacting neurons. Its supposed role in the nonsynaptic signal transmission of the brain

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Summary. Recent investigations confirm the importance of nonsynaptic signal tranmission in several functions of the nervous tissue. Present in various periventricular brain regions of vertebrates, the system of cerebrospinal fluid (CSF)-contacting neurons seems to have a special role in taking up, transforming and emitting nonsynaptic signals mediated by the internal and external CSF and intercellular fluid of the brain.

Most of the CSF-contacting nerve cells send dendritic processes into the internal CSF of the brain ventricles or central canal where they form terminals bearing stereocilia and a 9+0-, or 9+2-type cilium. Some of these neurons resemble known sensory cells of chemoreceptor-type, others may be sensitive to the pressure or flow of the CSF, or to the illumination of the brain tissue. The axons of the CSF-contacting neurons transmit information taken up by dendrites and perikarya to synaptic zones of various brain areas. By forming neurohormonal terminals, axons also contact the external CSF space and release various bioactive substances there. Some perikarya send their axons into the internal CSF, and form free endings there, or synapses on intraventricular dendrites, perikarya and/or on the ventricular surface of ependymal cells. Contacting the intercellular space, sensory-type cilia were also demonstrated on nerve cells situated in the brain tissue subependymally or farther away from the ventricles.

Among neuronal elements entering the internal CSF-space, *the hypothalamic CSF-contacting neurons* are present in the magnocellular and parvicellular nuclei and in some circumventricular organs like the paraventricular organ and the vascular sac. The CSF-contacting dendrites of all these areas bear a solitary 9x2+0-type cilium and resemble chemoreceptors cytologically. In electrophysiological experiments, the neurons of the paraventricular organ are highly sensitive to the composition of the ventricular CSF. The axons of the CSF-contacting neurons terminate not only in the hypothalamic synaptic zones but also in tel-, mes- and rhombencephalic nuclei and reach the spinal cord as well. The supposed chemical information taken up by the CSF-contacting neurons from the ventricular CSF may influence the function of these areas of the central nervous system.

Some nerve cells of the photoreceptor areas form sensory terminals similar to those of the hypothalamic CSF-contacting neurons. Special secondary neurons of the retina and pineal organ contact the retinal photoreceptor space and pineal recess respectively, both cavities being embryologically derived from the 3rd ventricle. The composition of these photoreceptor spaces is important in the photochemical transduction and may modify the activity of the secondary neurons. Septal and preoptic CSF-contacting neurons contain various opsins and other compounds of the phototransduction cascade and represent deep encephalic photoreceptors detecting the illumination of the brain tissue and play a role in the regulation of circadian and reproductive responses to light.

The *medullo-spinal CSF-contacting neurons* present in the oblongate medulla, spinal cord and terminal filum, send their dendrites into the fourth ventricle and central canal. Resembling mechanoreceptors of the lateral line organ, the spinal CSF-contacting neurons may be sensitive to the pressure or flow of the CSF. The axons of these neurons terminate at the external CSF-space of the oblongate medulla and spinal cord and form neurohormonal nerve endings. Based on information taken up from the CSF, a regulatory effect on the production or composition of CSF was supposed for bioactive materials released by these terminals. Most of the axons of the medullospinal CSF-contacting neurons and the magno- and parvicellular neurosecretory nuclei running to neurohemal areas (neurohypophysis, median eminence, terminal lamina, vascular sac and urophysis) do not terminate directly on vessels, instead they form neurohormonal nerve terminals attached by half-

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desmosomes on the basal lamina of the external and vascular surface of the brain tissue. Therefore, the bioactive materials released from these terminals primarily enter the external CSF and secondarily, by diffusion into vessels and the composition of the external CSF, may have a modulatory effect on the bioactive substances released by the neurohormonal terminals.

Contacting the intercellular space, sensory-type cilia were also demonstrated on nerve cells situated subependymally or farther away from the ventricles, among others in the neurosecretory nuclei. Since tight-junctions are lacking between ependymal cells of the ventricular wall, not only CSF-contacting but also subependymal ciliated neurons may be influenced by the actual composition of the CSF besides that of the intercellular fluid of the brain tissue.

According to the comparative histological data summarised in this review, the ventricular CSF-contacting neurons represent the *phylogenetically oldest* component detecting the internal fluid milieu of the brain. The neurohormonal terminals on the external surface of the brain equally represent an ancient form of nonsynaptic signal transmission.

Key words: CSF-receptors, Nonsynaptic signal tranmission, Neurohormonal terminals, Deep brain photoreceptors, Various vertebrates, Comparative fine structure, Immunocytochemistry

Introduction

By means of the silver impregnation technique, Landolt (1871) was the first to observe that the processes of some bipolar neurons of the amphibian retina cross the external limiting membrane and form enlargements, "Landolt's clubs" between the inner segments of photoreceptors. The space below the retinal pigment epithelium is a narrowed form of the embryonic optic ventricle, therefore - in a wide sense - we can regard the Landolt bipolars as the first described neurons of a CSF-contacting type (Vígh et al., 1983b, 1995b).

Later, similar nerve processes were observed in the third ventricle and the central canal (Studnicka, 1900; Kolmer, 1921; Agduhr, 1922). These processes belonged to subependymal neurons considered to be receptor cells. The peculiar location of these neuronal elements suggested that their activity may be connected with the CSF. Studying similar cells in the paraventricular organ, we called them liquor- or CSF-contacting neurons (Vígh et al., 1967, 1969; Vígh and Majorossy, 1968; Vígh, 1971). CSF-contacting neurons were also described in the preoptic recess organ (Vígh-Teichmann et al., 1969a,b, 1971a) and in another circumventricular organ, the vascular sac (Vígh et al., 1972) and further in the periventricular hypothalamic magnocellular and parvicellular nuclei (Vígh and Vígh-Teichmann, 1973; Vígh-Teichmann et al., 1976a; Nakai et al., 1979; Franzoni and Fasolo, 1982; Vígh-Teichmann and Vígh, 1983; Vígh and Vígh-Teichmann, 1998). There are only a few CSF-contacting neuronal elements in the mesencephalon (MacDonnell, 1983, 1989).

Similar to Landolt's bipolars of the retina, ciliated dendrite terminals are formed by some of the intrinsic pineal neurons. Furthermore, the retinal and pineal photosensory cells themselves are analogous to the CSF-contacting nerve cells in so far as they send dendritic processes into the pineal recess and the photoreceptor space of the retina, both being derived embryologically from diverticles of the third ventricle (Vígh-Teichmann and Vígh, 1985, 1986; Vígh and Vígh-Teichmann, 1988, 1989a,b). CSF-contacting nerve cells were also demonstrated in the wall of the lateral ventricles (Korf and Fahrenkrug, 1984; Petko and Ihionvien, 1989).

Finally, there are *axons* entering the internal and/or external CSF. Some of these axons are serotoninergic and their perikarya sit in the raphe nuclei (Parent, 1981). Intraventricular axons also terminate on CSF-contacting dendrites and perikarya and/or the ventricular surface of the ependyma. Others form neurohormonal terminals in the ventricles or facing the subarachnoidal CSF-space. All the above-mentioned neuronal elements represent components of the *CSF-contacting neuronal system of the brain* (Fig. 1).

In the present paper, we summarise recent and earlier data on the comparative neurohistology of neurons of various vertebrates related to the *internal* or *external* CSF and we also treat sensory-type neuronal cilia contacting the intercellular fluid (for detailed citation of earlier literature of CSF-contacting neurons see: Vígh, 1971; Vígh-Teichmann and Vígh, 1983, 1989; Vígh et al., 1998).

Starting with the neuronal elements contacting the internal CSF, we treat the hypothalamic nuclei and periventricular organs including the intraventricular axons and neuronal perikarya. Further we discuss the role of CSF-contacting neuron-like cells of photoreceptor areas. We also summarise data on the mechanoreceptor-like medullospinal and urophyseal CSF-contacting nerve cells.

1. CSF-contacting neurons of hypothalamic nuclei

CSF-contacting neurons are present in several magnocellular and parvicellular nuclei of the hypothalamus and in some periventricular organs. The neurosecretory nuclei may have direct contact with the inner CSF by dendritic processes and with the external CSF by their neurohormonal axon terminals. Some neurosecretory axons also enter the ventricular lumen (for axons to the external CSF-space, see chapter No. 6).

The magnocellular neurosecretory neurons in lower vertebrates (cyclostomes, fish, amphibians) form the preoptic nucleus and contain several CSF-contacting nerve cells in their hypendymal layer. The perikarya of the CSF-contacting neurosecretory cells are usually multipolar, they contain secretory granular vesicles and receive afferentations in form of axo-somatic and axo-

dendritic synapses (Vígh-Teichmann et al., 1976a). Many cells immunoreact with neurophysin, vasotocin, isotocin/mesotocin or enkephalin antibodies. Others show somatostatin-immunoreactivity. Besides, LHRH, TRH, alpha-MSH and CRF immunoreactivity was also demonstrated in some cells (lit. see in: Ray and Choudhury, 1990; Vígh and Vígh-Teichmann, 1998).

In higher vertebrates (reptiles, birds and mammals), the magnocellular neurosecretory cells form the supraoptic and paraventricular nucleus. No CSF-contacting dendrites were found in the supraoptic nucleus. In the *paraventricular nucleus* intraependymal as well as distal neurons send dendrites to the third ventricle (Fig. 2a-c). In reptiles and birds, the intraventricular ciliated dendritic terminals of the CSF-contacting neurons are ultrastructurally similar to those of the magnocellular preoptic nucleus of lower vertebrates (Vígh-Teichmann et al., 1970b). Their perikarya contain granular vesicles either of about 180 nm in diameter or smaller ones (diameter 100-110 nm) and contain immunoreactive neurophysin. Some of the CSF-contacting neurons show somatostatin immunoreactivity. Axonal processes of these cells run to the periventricular synaptic zones and contribute to pre- and postsynaptic structures (Vígh et al., 1981; Vígh-Teichmann and Vígh, 1983). Golgi-impregnation studies also revealed intranuclear fiber connections of CSF-contacting neurons in the paraventricular nucleus. As the magnocellular neurons are involved in the control of salt- and water balance, their receptory structures were viewed as osmosensitive elements (Korf et al., 1982, 1983; Korf, 1984).

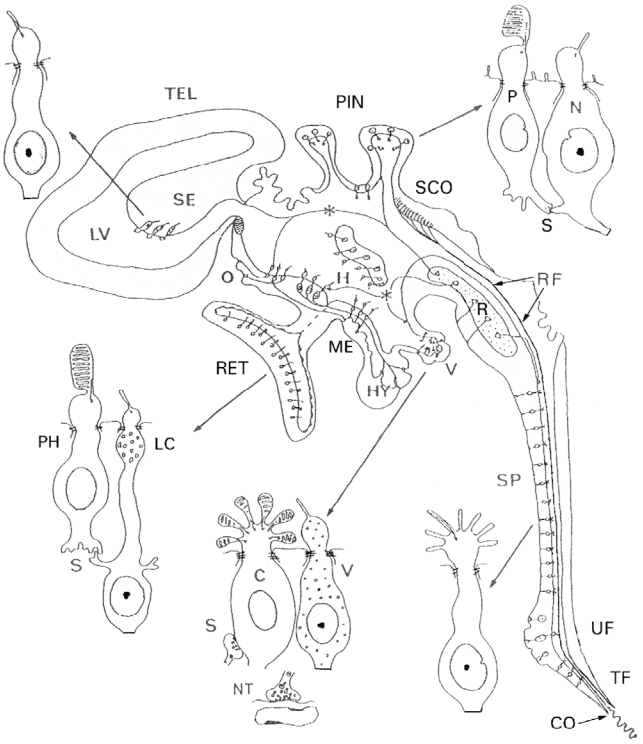

Fig. 1. Scheme of the CSF-contacting neuronal system of vertebrates. C: coronet cell, CO: caudal opening of the terminal filum, H: hypothalamic CSF-contacting neurons, HY: Hypophysis, LC: Landolt's club, LV: lateral ventricle, ME: median eminence, N: pineal CSF-contacting neuron, NT: neurohormonal terminal, O: vascular organ of the terminal lamina, P: pineal photoreceptor cell, PH: retinal photoreceptor cell, PIN: pineal organs, R: raphe nuclei, RET: retina, RF: Reissner's fibre, S: synapses, SE: septal area, SCO: subcommissural organ, SP: medullo-spinal CSF-contacting neurons, TEL: telencephalon, TF: terminal filum, UF: urophysis, V: CSF-contacting neurons of the vascular sac. Asterisks: intraventricular CSF-contacting axons.

The subependymal portion of the Gomori-negative magnocellular *nucleus lateralis tuberis* of fishes, forms extremely large intraventricular dendritic terminals containing granular vesicles (about 190 nm in diameter), Golgi areas and rough-surfaced endoplasmic reticulum (Fig. 2d,e). A second type, a small and strongly AChE-positive CSF-contacting neuron is also present scattered in the hypendymal layer and contains granular secretory vesicles of 60 nm in diameter. The large CSF-contacting neurons contain ACTH, immunoreactive neuropeptide Y, calbindin and FMRF-amide (Vallarino and Ottonello, 1987; Rodrigues-Moldes et al., 1990; Chiba et al., 1991, 2002; Subhedar et al., 1996). Supraependymal axons form multiple axo-dendritic synapses on the CSF-contacting dendritic terminals of both types of neurons (Vígh-Teichmann and Vígh, 1974, 1983; Vígh-Teichmann et al., 1970a,c). Hypophysectomy causes retrograde degeneration in the medial portion of the nucleus lateralis tuberis (Zambrano, 1970). Coto-Montes and coworkers (1994) demonstrated immunoreactivity for corticotropin-releasing factor in the CSF-contacting cells of the nucleus lateralis tuberis. Therefore, these cells may influence the release of corticotropins from the adenohypophysis in function of the actual state of the CSF.

Concerning the parvicellular hypothalamic nuclei, the presence of CSF-contacting neurons suggests a similar relation to the ventricular CSF as we have seen in the magnocellular neurosecretory nuclei. Ciliated ventricular dendrites were found in the anterior periventricular nucleus and in the infundibular nucleus of various vertebrates. The CSF-contacting neurons of the parvicellular preoptic nucleus are described in the chapter on circumventricular organs (see: preoptic recess organ).

In the *anterior periventricular nucleus* - extending behind the optic chiasm - CSF-contacting neurons were found in various numbers in bony fishes, amphibians and reptiles. Perikarya and axons exhibited AChE reaction. Axons of the CSF-contacting neurons of the eel were seen to contribute to an AChE-positive fiber tract that passes to the proximal neurohypophysis. Similar axons were traced using silver impregnation in the lizard (Vígh-Teichmann et al., 1976b; Fasolo and Franzoni 1983; Vígh-Teichmann and Vígh, 1983).

In the carp, two types of CSF-contacting neurons can be distinguished by the size of the granular vesicles

present in them (either 80 or 110 nm in diameter). The neurons receive at least three types of afferents (axons with granular vesicles measuring either 80 nm or 110 nm, or synaptic vesicles only). There are somatostatin-immunoreactive CSF-contacting neurons scattered among immunonegative cells. The basal processes of the immunoreactive cells contribute to a strong somatostatin-positive fiber plexus extending to the proximal neurohypophysis and to the lateral and the mamillary recess. Since somatostatin is an inhibitory

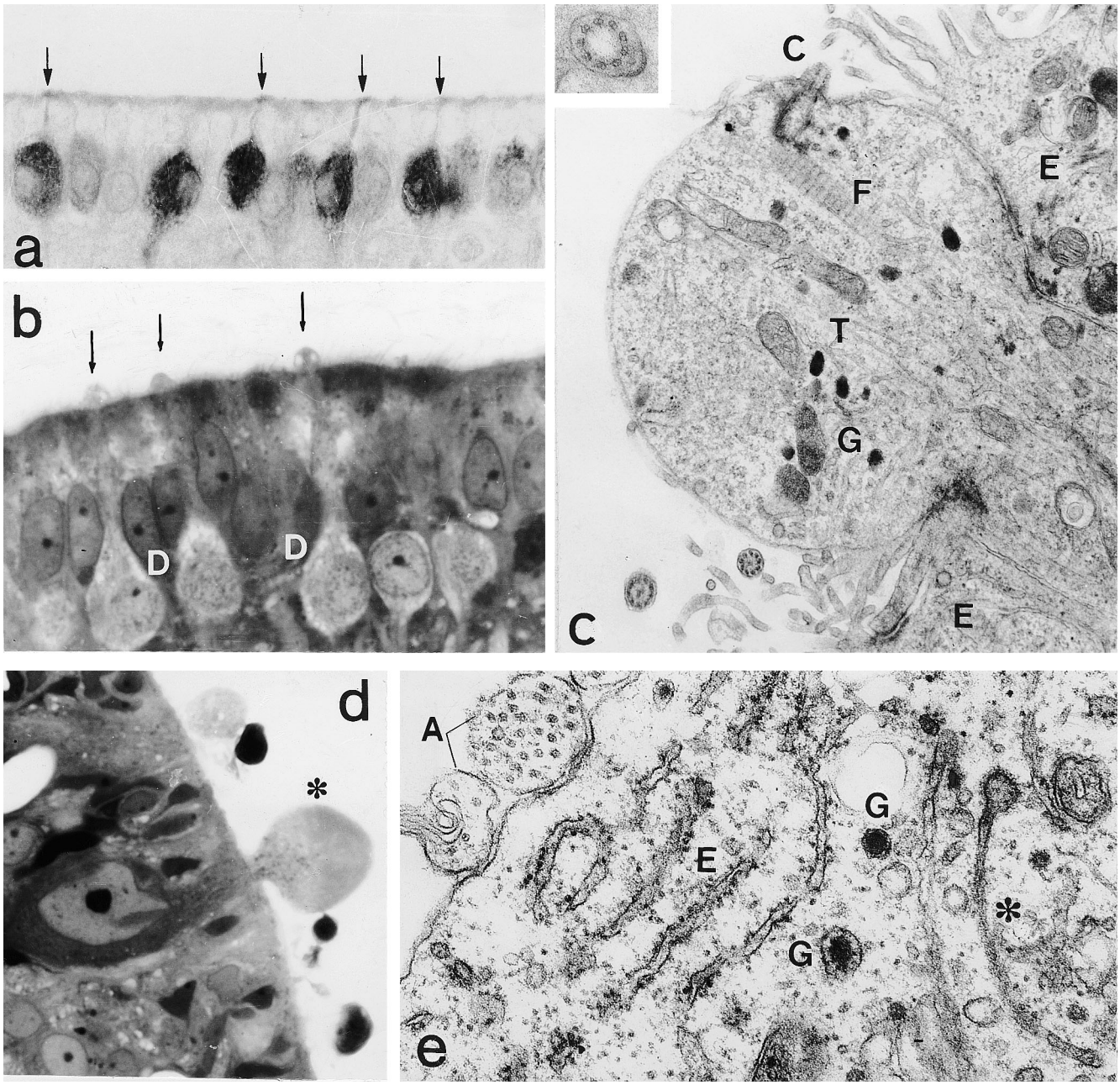

Fig. 2. a. Intraependymal CSF-contacting neurons (arrows) of the paraventricular organ of the turtle Emys orbicularis, somatostatin immunoreaction, x 420. **b.** Distal perikarya (D) sending their dendrites (arrows) to the ventricle. x 11,00. **c.** Dendritic terminal (T) of a neurosecretory cell of the paraventricular nucleus of the turtle, *Emys orbicularis*, C: cilium, E: ependymal cells, G: granular vesicles, F: rootlet fiber. x 22,800. Inset: Cross section of a 9+0-type cilium of the CSF-contacting dendrite. x 36,000. **d.** Large dendritic CSF-contacting terminal (asterisk) of a hypendymal neuron of the nucleus lateralis tuberis of the carp (*Cyprinus carpio*). Semithin section, toluidine blue staining. x 320. **e.** A part of the large dendritic terminal of the nucleus lateralis tuberis. A: intraventricular axons, E: endoplasmic reticulum, G: granular vesicles, asterisk: Golgi area. x 48,000

neuropeptide, the role of the somatostatin-immunoreactive nerve fibers is thought to be connected with CSF-dependent inhibitory mechanisms (Vígh-Teichmann et al., 1983a).

In the submammalian *infundibular nucleus*, the number of CSF-contacting cells is high in amphibians (Fig. 3a) and reptiles but decreases in birds. In Triturus vulgaris, the presence of about 46,000 CSF-contacting

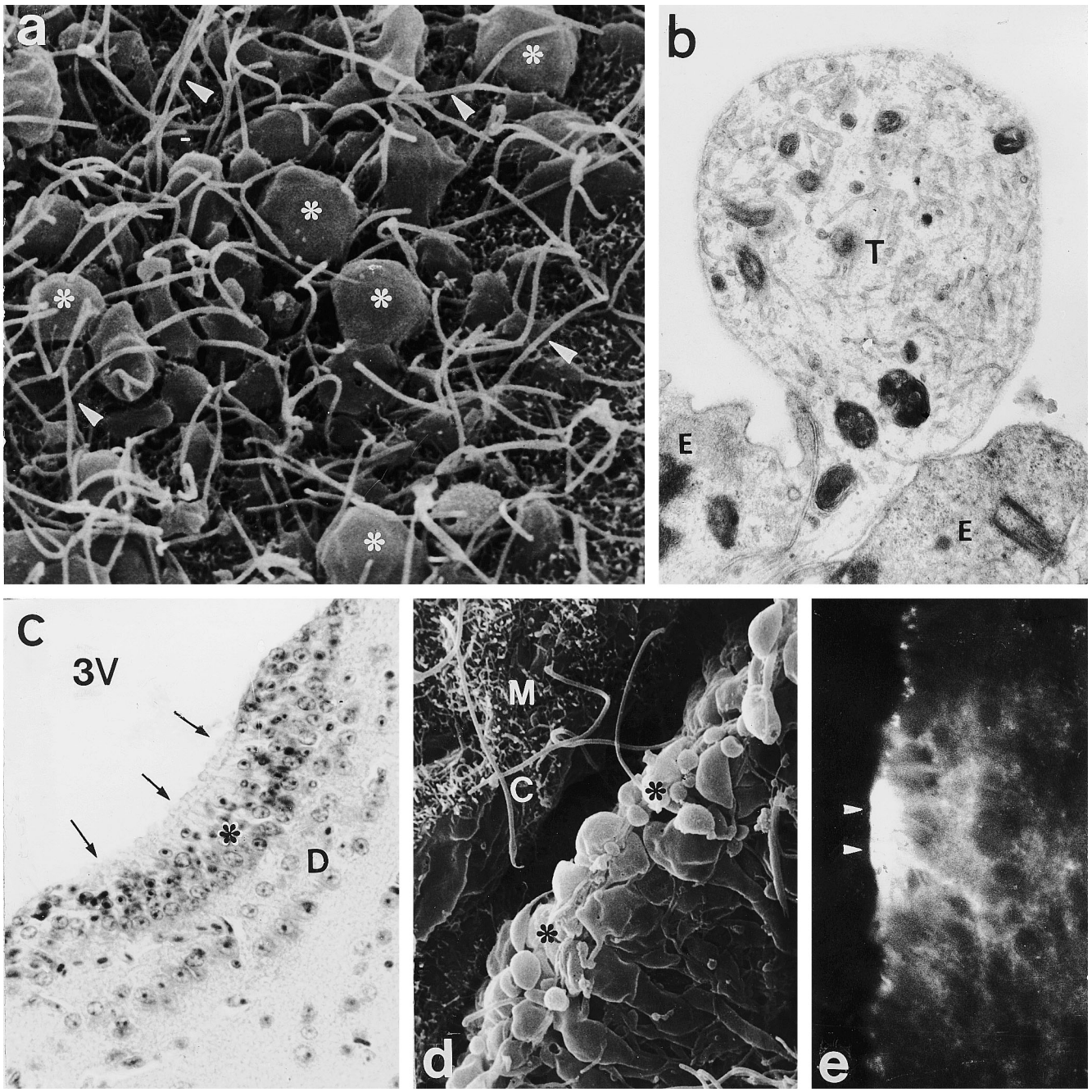

Fig. 3. a. Scanning electron microscopic picture of the intraventricular dendritic terminals (asterisks) of the infundibular nucleus of the turtle (*Pseudemys scripta elegans*). Arrowhead: ependymal kinocilia, x 7,200. **b.** CSF-contacting nerve terminal (T) in the infundibular recess of the Guinea pig. E: ependymal cells. x 26,400. **c.** The proximal (asterisk) and distal (D) part of the nucleus of the paraventricular organ of the chicken. 3V: 3rd ventricle, arrows: intraventricular dendritic terminals, chromehaematoxylin staining. x 850. **d.** Scanning electron microscopic picture of the intraventricular dendrites connected by nerve fibers (asterisks), C: ependymal cilia, M: ependymal microvilli. x 7,200. **e.** Induced monoamine fluorescence in the ventricular dendrites (arrowheads) of the paraventricular organ of the frog (*Rana esculenta*). x 850

dendritic terminals were estimated in the infundibular nucleus. Intraventricular axons form axo-dendritic synapses on the dendrite terminals. The great variety of synaptic contacts (presynaptic granular vesicles measuring either about 80-110 or 130-170 nm) around the CSF-contacting neurons suggest the existence different interneuronal and afferent connections (Vígh-Teichmann and Vígh, 1974, 1979). In cartilagineous fish, infundibular CSF-contacting neurons containing dense-core vesicles ranging in diameter between 100 and 120 nm were presumed to be aminergic, while those containing granular vesicles ranging in diameter between 160 and 180 nm were presumed to be peptidergic (Kotrschal et al., 1985). In birds, only one type of CSF-contacting nerve cell could be demonstrated in the infundibular nucleus (granular vesicles: 130-140 nm in diameter, Vígh-Teichmann et al., 1971b).

Some of the infundibular CSF-contacting neurons contain AChE, while in others somatostatin, tyrosine hydroxylase, 5HT, gastrin or VIP were found (Yamada et al., 1982; Vígh-Teichmann and Vígh, 1983; Franzoni et al., 1986; Fasolo et al., 1986; Wright, 1986). Lopez-Avalos and coworkers (1993) described the presence of immunoreactive corticotropin-releasing factor in the infundibular nucleus and traced immunoreactive fibers to the median eminence. Galanin-immunoreactivity was found in the CSF-contacting infundibular neurons of the turtle (Jiménez et al., 1994); the authors assume a hypophysiotropic and/or central role of galanin in this nucleus.

Concerning the CSF-contacting neuronal elements of the *arcuate nucleus of mammal*s, several intraventricular dendrites were found in the infundibular recess of the rat and guinea pig (Fig. 3b). They contained granular vesicles of various sizes (diameter measuring either 110-140 or 180-200nm). Further, some intraependymal neurons of the arcuate nucleus of the hedgehog contact the CSF, their basal processes running into the subependymal neuropil (Vígh-Teichmann et al., 1981). There are several perikarya in mammals sendig a 9+0-type cilium into the intercellular space and they may have a special role in percepting modulations of the intercellular fluid (see in chapter No. 7).

2. CSF-contacting neurons of circumventricular organs

Among circumventricular organs the first described CSF-contacting neuronal area was the paraventricular organ, a bilateral structure in the hypothalamus of submammalian vertebrates. CSF-contacting neurons are also present in the vascular sac that evaginates caudally from the infundibulum of fishes. Besides these two periventricular organs, we want to treat the CSF-contacting neuronal area of the preoptic recess *(preoptic recess organ*) as well as the so-called mesencephalic midline ridge formation in this chapter.

The *paraventricular organ* is a rather complex CSF-contacting neuronal area of the hypothalamus. It is composed of a special columnar ependyma and of CSF-contacting neurons, forming the "nucleus organi paraventricularis" (Fig. 3c). This nucleus consists of an intra-/subependymal layer of bipolar neurons and of a distal group of multipolar perikarya, both groups sending dendritic terminals into the ventricle. Connected by intraventricular axo-dendritic synapses, numerous nerve fibers and some free cells can be found close to the intraventricular dendritic endings (Fig. 3d). Underlining the receptor character of these cells, somatodendritic synapses were described on neurons of the paraventricular organ of frogs (Röhlich and Vígh, 1967; Vígh et al., 1967, 1969; Vígh and Majorossy, 1968; Vígh, 1971; Peute, 1971;Vígh and Vígh-Teichmann, 1973; Nakai et al., 1977, Vígh-Teichmann et al., 1979; Sano et al., 1983; Sänger et al.,1983; Vígh-Teichmann and Vígh, 1983, 1989).

Several bioactive compounds were demonstrated in the neurons of the organ (Fig. 3e), like noradrenaline, dopamine, L-dopa, 5-hydroxytryptamine, tyrosine hydroxylase, neuropeptide Y, vasoactive intestinal protein, substance P, somatostatin, nitric oxide synthase and galanin (Vígh and Vígh-Teichmann, 1973; Blähser et al., 1982; Gonzalez Nicolini et al., 1995; Lowry et al., 1996; Dicke et al., 1997; Adrio et al., 1999; Ubink et al., 1999). Immunolocalization of catecholamine enzymes has also been reported in the CSF-contacting neurons (Batten et al.,1993; Ma and Lopez, 2003). However, some authors failed to detect these synthesizing enzymes and discused the possible role of the organ in the intraventricular uptake and/or transport of biogenic amines (Guglielmone, 1995; Meek, 1999).

A colocalization of NPY-immunoreactivity and that of Phe-Met-Arg-Phe-NH2 (FMRF-amide) was described in the neurons of the organ (Vecino and Ekström, 1992). Distal neurons contain immunoreactive GABA in amphibians (Franzoni and Morino, 1989). Immunocytochemical studies also revealed the presence of gastrin-, met-enkephalin- and beta-endorphin-containing cells in the organ of fish, frog and bird (lit. in Vígh-Teichmann and Vígh, 1983). The distal group of neurons exhibit acetycholinesterase activity and immunoreact with choline acetyltransferase (Vígh-Teichmann et al., 1970a; Ekström, 1987). The expression of NADPH-diaphorase activity in the neurons of the paraventricular organ was explained by their involvement in cholinergic circuits and in the control of hormone regulation (Villiani and Guarnieri, 1995; Meek, 1999). The excitatory amino acid glutamate is also present in the nucleus of the paraventricular organ (Vígh and Vígh-Teichmann, 1998).

Alpha-melanophore-stimulating hormone and non-acetylated endorphin coexists in the cells of the paraventricular organ (Tuinhof et al., 1998). Melanin-concentrating hormone (MHC), corticotropin-releasing hormone (CRF) and gonadotropin-releasing hormone (GnRH) found in these neurons of various species may exert neuromodulatoy and/or neurotransmitter activities (Fellmann et al., 1984; Mancera et al., 1991; Lopez-

Avalos et al., 1993; Muske and Moore, 1994; Collin et al., 1995; Rastogi et al., 1998; Silveira et al., 2001). A marked change in secretion of MHC associated with metamorphosis of the lamprey was explained by its supposed role in feeding or osmoregulation (Bird et al., 2001). The paraventricular organ also possesses the steroidogenic enzyme 3betaHSD and therefore may produce progesterone (Sakamoto et al., 2001).

In the synaptic zone between the two groups of neurons, the axons or axon collaterals of the intra- and subependymal nerve cells join the dendrites of the distal cells, as concluded from silver impregnated preparations. The existence of afferent axons derived from outside the paraventricular organ can also be assumed. A dense plexus of FMRFamide immunoreaction was found around the paraventricular organ by Krishna and Subhedar (1992). The arborization pattern of the monoamine-containing axons of the hypendymal paraventricular neurons showed that they terminated not only around the distal perikarya of the organ but also in the fibrous zone of the lateral hypothalamus.

Several fiber tracts originate from the paraventricular organ. Aminergic fibers join the medial forebrain bundle, while AChE-positive fibers run in the lateral forebrain bundle (Parent and Northcutt, 1982; Vígh-Teichmann and Vígh, 1983; Johnston et al., 1990). In the chicken, the AChE-positive fiber bundle runs to the thalamus. Monoamine-containing fibers of the organ were found to terminate in the median eminence (Parent, 1981) and to innervate the pars intermedia of the pituitary (Prasada Rao, 1982). Furthermore, axons were traced to isodendritic neurons of the lateral hypothalamus (Vígh-Teichmann and Vígh, 1977).

Ascending projections to hypothalamic and extrahypothalamic areas of the organ are particularly well developed in the lungfish (Bartheld and Meyer, 1990). Major targets include the dorsal hypothalamus, the periventricular preoptic nuclei, the habenula, the subhabenular region, the anterodorsal thalamus and telencephalic septum. Most ascending fibers follow the medial forebrain bundle and others course in the fasciculus retroflexus and terminate in rostral parts of the ipsilateral habenula. Descending fibers run to the synaptic zones of the mesencephalic tegmentum, ventral tectum, isthmic region, ventral portions of the reticular formation of the whole rhombencephalon and some fibers also extend into the spinal cord.

Following lesions of the paraventricular organ, degenerating axons and nerve terminals were observed in the rostral pars distalis of the hypophysis, further in the proximal pars distalis and in the neurointermediate lobe of the goldfish (Fryer et al., 1985). The CSF-contacting neurons of the paraventricular organ of catfish send fibers retrogradely labeled with cobaltous lysine to the pituitary stalk (Prasada Rao et al., 1993). Degeneration experiments in the newt established the existence of a fiber projection from the CSF-contacting neurons to the striatum. Lesions of the organ resulted in alteration of motoric behaviour (Dube et al., 1990).

Administration of $CaCl_2$, NaCl, and $NaHCO_3$ into the lateral ventricle of chickens and sparrows resulted in an increase of induced monoamine fluorescence in the organ. Electrical recordings of neural activity in and near the paraventricular organ show continuous and phasic, spontaneous activity of its neurons. After exchange of CSF for an artificial fluid, the spontaneous activity of the recorded neurons diminished, underlining the sensitivity of CSF-contacting neurons to alteration in the composition of the CSF. We can suppose that the numerous neurons containing different mediator substances detect different parameters of the CSF and via several efferentations of the organ influence the activity of the central nervous system from the telencephalon to the spinal cord (George and Meissl, 1987; Vígh and Vígh-Teichmann, 1998).

CSF-contacting neurons of the posterior recess may represent the caudal continuation of the paraventricular organ. Situated in the folded posterior recess of the hypothalamus, it has a high number of aminergic CSF-contacting neurons, especially in cartilagineous fishes. These neurons contain monoamines and neuropeptide-Y and their axons terminate in the neuropile of the hypothalamus (Kotrschall et al., 1985b; Rodriguez-Moldes and Anadon, 1987; Chiba et al., 2002; Adrio et al., 1999; Ma and Lopez, 2003).

Following lesions of the nucleus of the posterior recess, degenerating axons and terminals were observed in the rostral and proximal pars distalis but not in the neurointermediate lobe of the pituitary in goldfish (Fryer et al., 1985). CSF-contacting neurons of this nucleus retrogradely labeled with cobaltous lysine were found to project into the pituitary stalk of catfish (Prasada Rao et al., 1993).

In birds, bipolar serotonin immunoreactive CSF-contacting neurons are present in the caudalmost wall of the third ventricle, in a localization similar to that of the nucleus of the posterior recess (Hirunagi et al., 1992).

The *wavy paraventricular ependyma* of the third ventricle of *mammals* was earlier regarded as homologon to the paraventricular organ of submammalians (lit. See: Vígh, 1971; Vígh-Teichmann and Vígh, 1983). This ependymal area is not uniformly developed in the various mammals studied. It contains only a few subependymal nerve cells in the cat. There are more numerous neurons in the insectivorous hedgehog and marsupial opossum in this area. In the hedgehog some of the intraependymal neuronal perikarya contact the CSF and may correspond to the CSF-contacting neurons of submammalian vertebrates (Vígh-Teichmann et al., 1981; Vígh and Vígh-Teichmann, 1998). An equivalent of the paraventricular organ of submammalians was reported to have been identified in the human fetus as well (Trandafir et al., 1983).

Preoptic recess organ. The rostral part of the parvocellular preoptic nucleus extends to the terminal lamina and dorsally to the foramen of Monro. In this periventricular area - considered by some authors as

telencephalon medium - CSF-contacting neurons were found (Fig. 4a) in a circumventricular organ-like arrangement among ependymal cells in amphibians (Vígh-Teichmann et al., 1969a,b, 1971a). Scanning electron microscopy revealed numerous intraventricular terminals in the preoptic recess, each bearing a short solitary cilium (Vígh-Teichamnn et Vígh, 1979).

Formaldehyde-induced fluorescence immunoreactivity and high performance liquid chromatography demonstrated the presence of monoamines in these neurons of various species (Vígh-Teichmann et al., 1969b; Nakai et al., 1977; Ueda et al., 1984; Kotrschal et al., 1985; Corio et al., 1992; Lowry et al., 1996). In addition, GABA- and galanin-immunoreactive CSF-contacting neurons were found in the same area (Franzoni and Morino, 1989; Olivereau and Olivereau, 1992).

By means of silver impregnation, the axons of the preoptic CSF-contacting neurons could be traced to the periventricular neuropil of the hypothalamus (Parent 1981; Shimizu et al., 1983). Iontophoretic injection of peroxidase into the neural lobe of the toad pituitary resulted in labeling of nerve cells located very close to the ependyma of the preoptic recess (Pasquier et al., 1980). Axons of the preoptic recess organ also may participate in the innervation of the pars intermedia of the hypophysis. Monoamine fluorescence of the organ was found to be more intense in black-adapted frogs than in white adapted ones, a result suggesting a control of the release of melanocyte-stimulating hormone of the pars intermedia (Prasada Rao, 1982). White-background adaptation was not observed after extirpation of the preoptic recess organ in developing animals (Kouki et al., 1998). Using in situ hybridization and immunocytochemistry, pro-opiomelanocortin, alpha- and gamma-MSH, non-acetylated endorphin was detected in the neurons of the anterior preoptic area of Xenopus (Tuinhof et al., 1998). A melanocyte-regulating function may also be connected to the opsin content of some preoptic CSF-contacting neurons (see also: deep encephalic photoreceptors in chapter No. 4).

CSF-contacting neurons were also described in the *parvicellular preoptic nucleus of cyclostomes, fish and reptiles* (Parent, 1981; Shiga et al., 1989). Tyrosine hydroxylase immunoreactivity indicating the local synthesis of catecholamines, was demonstrated in CSF-contacting neurons around the preoptic recess of the reptile, Caiman crocodilus, by Brauth (1988).

Ultrastructurally, the intraependymal and subependymal neurons of the parvicellular preoptic nucleus form relatively large intraventricular dendritic terminals and contain granular vesicles, about 80-95 nm in diameter. Their axons could be traced by silver impregnation to the adjacent neuropil of the hypothalamus of the turtle (Parent, 1981). Synapses found on the CSF-contacting neurons were characterized by synaptic vesicles and granular vesicles measuring either 80-110 or 130-170 nm in Emys orbicularis. The different types of afferent axon terminals confirm the expression of different synaptic transmitters influencing the activity of the parvicellular preoptic CSF-contacting neurons (Vígh-Teichmann and Vígh, 1983).

In mammals (guinea pig, cat, hedgehog and opossum), supraependymal cells and fibers were observed on the ependymal lining of the parvicellular preoptic nucleus, and ciliated perikarya around the preoptic recess. The subependymal ciliated neurons may be derived from the CSF-contacting neurons of lower vertebrates (see also chapter No. 7.).

The *vascular sac* of *fish* evaginates from the dorsal wall of the infundibulum and forms several epithelial pouches surrounded by vessels.The epithelium of the vascular sac is formed by ependymal cells; among them the so-called coronet cells and CSF-contacting neurons (Vígh-Teichmann and Vígh, 1983).

The *coronet cells* (Fig. 4b) have a luminal process bearing several bulb-like cilia. The cilia are filled with parallely arranged tubular cisternae (Vígh et al., 1972; Follenius, 1982). The ultrastructure of the perikarya is characterized by abundance of smooth endoplasmic reticulum showing immunoreaction for parathyroid hormone-related protein (Devlin et al., 1996). There are afferent axo-somatic synapses on the basal part of the coronet cells (Vígh and Vígh-Teichmann 1977). In some of the nerve fibers of the organ immunoreactive neuropeptide Y was demonstrated (Chiba et al., 2002).

The coronet cells and the CSF-contacting neurons present in the organ display a medium content of immunoreactive glutamate (Vígh and Vígh-Teichmann, 1998). The neuronal character of the coronet cells is still under debate since an efferent axon or synapse formed by the cells have not yet been demonstrated, but a nonsynaptic efferentation of these cells is also possible. Earlier authors considered the coronet cells as mechanoreceptors that would inform the brain about the deepth of water (for literature see Leonhardt, 1980). The coronet cells may also be involved in transcellular ion transport for the CSF (Jansen et al., 1982). Calcium-sensitive receptors were demonstrated in the coronet cells by in situ hybridization (Flanagan et al., 2002).

The presence of *CSF-contacting neurons* in the vascular sac indicates a complex receptor function of the organ. These neurons were first demonstrated by light microscopy as AChE-positive perikarya scattered among the coronet cells and ependymal cells (Vígh-Teichmann et al., 1970a). The CSF-contacting neurons are bipolar and their intraventricular dendritic terminals - like similar hypothalamic endings - are supplied with 9x2+0 cilia. In teleost species, their dendritic terminals and corresponding somata contain granular vesicles (diameter 80-90 nm, or 150 nm). The perikarya show immunoreactrivity for neuropeptide Y, gamma-aminobutyric acid and glutamic acid decarboxylase (Yáñez et al., 1997; Chiba et al., 2002). There are two types of axo-somatic synapses on the CSF-contacting neurons, both similar to those terminating on coronet cells. As revealed by the AChE reaction, the basal processes of the CSF-contacting neurons contribute to

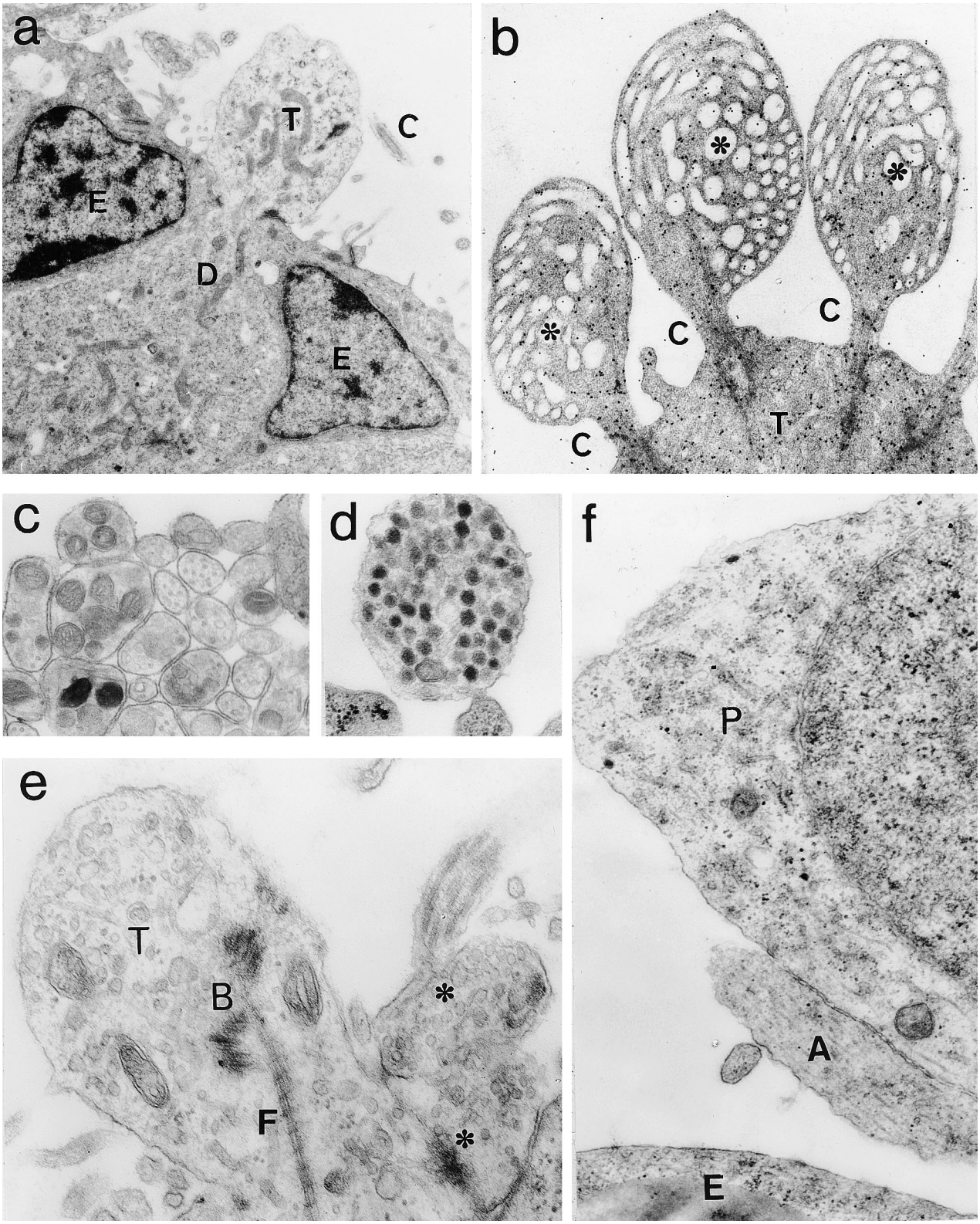

Fig. 4. a. Dendrite (D) and intraventricular terminal (T) of a CSF-contacting neuron in the preoptic recess of the lamprey (*Petromyzon fluviatilis*). C: cilium, E: ependymal cells. x 39,000. **b**. CSF-contacting terminal (T) with bulbous cilia (C) of the coronet cell in the lumen of the vascular sac. asterisk: tubuli of the bulbous cilia, glutamate immunoreaction (black dots of immunogold particles). x 16900. **c.** Intraventricular axons of the infundibular recess of the Guinea pig. x 27,600. **d.** Intraventricular nerve fiber containing granular vesicles of 120nm in diameter in the infundibular recess of the rat. x 23,600. **e.** Axon terminals (asterisks) on an intraventricular dendrite terminal (T) of the CSF-contacting neuron of the periventricular nucleus in the carp (*Cyprinus carpio*). B: basal bodies, F: rootlet fiber. x 43,200. **f.** Intraventricular axon (A) and perikaryon (P) in the infundibular recess of the newt (Triturus cristatus). E: ependymal cell. x18,800

the fibers of the *nervus sacci vasculosi*. The latter can be traced by means of their AChE activity to the *nucleus (ganglion) sacci vasculosi* and to the level of the ventral thalamus (Vígh et al., 1972, Vígh and Vígh-Teichmann, 1977).

By perfusion fixation the blood is washed out from capillaries of the brain but remains in the large sinusoids of the vascular sac, a pattern indicating an individual circulation of the organ. In some cartilagineous fish perivasal rings of smooth muscle cells are present (Vígh, 1971) that enable the control of the quantity of blood present in the sinusoids. In the ray the basal process of the CSF-contacting neurons filled with large granular vesicles contacts the basal lamina of the vascular surface of the organ. At these sites, a neurohormonal release into the perivascular space was proposed (Vígh-Teichmann and Vígh, 1983). In the nerve fibers of the organ, immunoreactive thyrotropin-releasing hormone was demonstrated (Teijido et al., 2002).

The mesencephalic middle ridge formation is a circumventricular organ-like area situated on the ventricular surface of the optic tectum in cartilaginous fishes (MacDonnell, 1983). As part of the mesencephalic trigeminal complex, it contains several large CSF-contacting neurons and supraependymal perikarya as well as nerve fibers. On the basis of the relationship of axonal varicosities and terminals to CSF-contacting neurons, a nonsynaptic association was suggested between these elements (MacDonnell, 1989). CSF-factors influencing these CSF-contacting structures might serve to alter the excitability of the mesencephalic trigeminal complex, and thus, regulating the intensity of biting reflexes in sharks (MacDonnel, 1983).

3. Intraventricular axons and neuronal perikarya

Supraependymal neurons and intraventricular axons were found in the inner CSF from cyclostomes to mammals (Fig. 4c-f). With scanning electron microscopy perikarya and varicose fibers of various calibers have been seen among the cilia and microvilli of the ependymal surface (Tulsi, 1979; Vígh-Teichmann et al., 1980b, 1981; Leonhardt, 1980; Chiba et al., 1981; Mestres, 1981; Mestres and Rascher, 1981, 1994; Hirunagi et al., 1989; MacDonnell, 1989). Supraependymal 5-HT nerve fibers were found in the human brain as well (Richards et al., 1981).

In mammals, there are several nerve cells of various type (uni-, bipolar, pseudounipolar and multipolar) located singly or in groups in the infundibular and mamillary recesses. Axons of these nerve cells cross the ependymal lining and enter the periventricular synaptic zone (Vígh-Teichmann et al., 1980b). Regarding the abundance of its supraependymal structures, the mamillary recess shows close similarity to the infundibulum: glial cells, macrophages, neuronal complexes, single neurons and nerve fibers occur in the ventricular lumen (Vígh-Teichmann et al., 1981). Nearly all glia cell types present in the brain tissue also occur in the ventricular cavity. CSF-contacting perikarya and fibers are present in other brain areas e.g. in the mesencephalon of cartilaginous fishes as well (see: mesencephalic midline ridge formation) and above the lateral aperture of the 4th ventricle (Leonhardt and Lindemann, 1973). Several CSF-contacting nerve fibers run among intraventricular dendrites of the paraventricular organ.

Intraventricular axons are more abundant in mammals than in submmalians. Two main types of supraependymal axon terminals are generally found, one of them forms synaptic contacts on intraventricular dendrites and neuronal perikarya, or innervates the luminal surface of the ependyma. Axons innervating the free surface of the ependyma are present in the pineal recess as well (Vígh-Teichmann et al., 1973; Welsh et al., 1989). Some CSF-contacting axons are serotoninergic, their perikarya being situated in the raphe nuclei (Parent, 1981).

The other type of axon terminal is a free, bulb-like ending without any synaptic contact. Axons of magnocellular neurosecretory nuclei were also traced to the lumen of the infundibular recess, and terminate there freely in the CSF. The large secretory vesicles of these CSF-contacting axons contain immunoreacting neurophysin. A nonsynaptic, neurohormonal release of neurosecretory substances into the CSF by these terminals was supposed (Vígh and Vígh-Teichmann, 1998; Frank et al., 2002). Neurohormonal axon terminals of various neurosecretory nuclei contacting the external CSF space are descibed in chapter No. 6.

4. CSF-contacting neurons of photoreceptor areas

Retinal CSF-contacting neuronal elements

As already mentioned in the introduction, the *Landolt-clubs* are thickenings of dendrites of some small bipolar neurons of the retina (Fig. 5a,b). These terminal dendrite thickenings contain several mitochondria and lie between the inner segments of the rods and cones in the photoreceptor space embyologically derived from the optic ventricle of the diencephalon. These dendritic terminals are provided with a short solitary 9x2+0-type cilium and structurally do not differ from the CSF-contacting dendritic terminals of the hypothalamus (Dacheux, 1982; Vígh et al., 1983b; Quesada and Genis-Galvez, 1985).

Besides their main dendrite running to the surface, the Landolt bipolars have dendritic side-ramifications that receive synapses from photoreceptor cells. The axons of the Landolt bipolars run to the internal plexiform layer. Therefore, with regard to their synaptic connections, Landolt bipolars are similar to other bipolars of the retina: they seem to transmit photic information received by the photoreceptors. Landolt's bipolars contain immunoreactive glutamate in a considerable quantity, similar to the retinal rods and cones, but no rhodopsin immunoreaction was found in

them (Vígh et al., 1995a,b,). In the regenerating retina of the newt, Landolt bipolars produce new photoreceptors (Grigorian, 1996). The chemical composition of the interphotoreceptor space is important for the circulation of some components of the phototransduction cascade; information taken up from this fluid space was supposed to modify the activity of Landolt bipolars (Vígh et al., 2002).

The inner segments and in a wider sense, also the outer segment of photoreceptors developed from a 9+0-type cilium and sitting in the photoreceptor space derived from the optic ventricle - are also homologous with the dendritic terminals of CSF-contacting neurons (Vígh et al., 1983b). Retinal outer segments when damaged (e.g. by detachment from the pigment epithelium) dedifferentiate within a short time to a smooth cilium. The shape of the receptor pole of dedifferentiated rods and cones is identical to that of CSF-contacting neurons.

Pineal CSF-contacting neuronal elements.

In most of the species investigated, the photoreceptor outer segment of the mammalian pinealocytes is represented by a simple sensory cilium of 9x2+0-type. In some species like the ferret, the cilia develop outer-segment-like structures (Vígh and Vígh-Teichmann, 1993). Measuring the light intensity of the

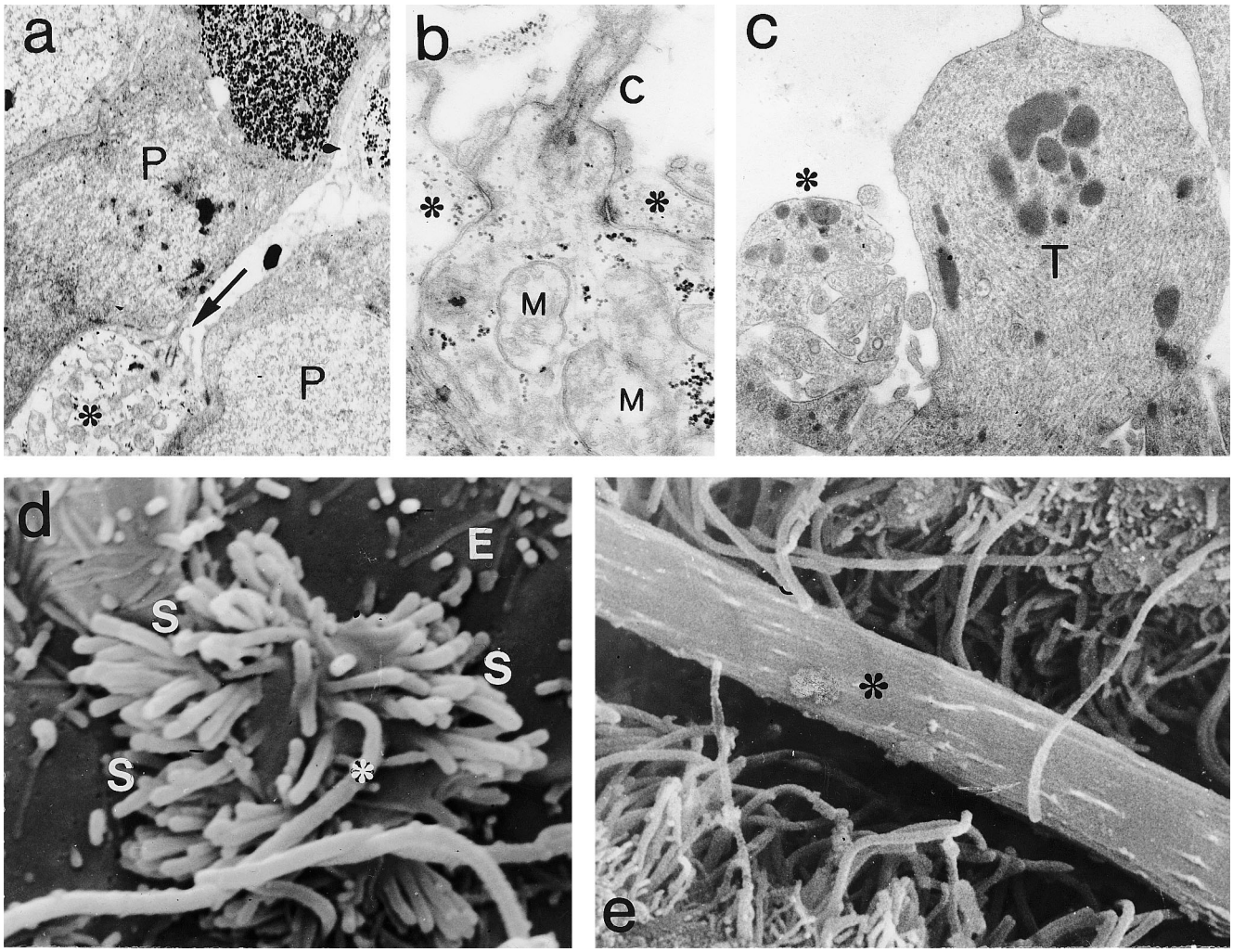

Fig. 5. a. Dendrite enlargement (Landolt's club) containing several mitochondria (asterisk) of a retinal bipolar cell of Triturus cristatus protrudes into the photoreceptor space (arrow), P: photoreceptor cells, x 9,400. **b.** The ciliated (C) dendrite terminal of the Landolt bipolar with higher magnification. M: mitochondria, asterisks: Mullerian cells. x 28,600. **c.** Bulb-like terminal (T) of a pinealocytic process of the opossum *(Didelphis virginiana*) in the pineal recess, asterisk: CSF-contacting axons, x 14,600. **d:** scanning electron microscopic picture of the stereocilia (S) and kinocilium (asterisk) of a CSF-contacting neuron of the oblongate medulla in the turtle (*Pseudemys scripta elegans*), E: ependymal surface. x 10,000. **e:** scanning electron microscopic picture of Reissner's fiber (asterisk) running freely in the central canal of the oblongate medulla in the carp *Cyprinus carpio*, x 12,000

environment, the pineal organs of submammalian vertebrates contain photoreceptive pinealocytes with cone- and rod-like outer segments. Similarly to the interphotoreceptor space of the retina, the pineal lumen of submammalians also develops from diverticles of the 3rd ventricle, and the pineal photoreceptor cells - protruding with their receptor pole into the lumen of the pineal recess (Fig. 5c) - exhibit a CSF-contacting-like character (Vígh et al., 1975, 1997, Vígh and Vígh-Teichmann, 1988, 1992; Vígh-Teichmann and Vígh, 1992). In amphibians, a group of pineal photoreceptor cells, situated around the base of the organ, remains on the top of the 3rd ventricle (Vígh-Teichmann et al., 1980a). Also in some mammals, the suprapineal recess and the central zone of the intrapineal recess contains pinealocytes which directly contact the CSF; a melatonin-release into the internal CSF has been supposed for these cells (Hewing, 1982; Welsh et. al., 1989; Vígh and Vígh-Teichmann, 1993).

The pineal organ of lower vertebrates contains neurons similar to Landolt bipolars. The subependymal neuronal perikarya of some cartilagineous fishes send ciliated dendrites into the lumen of the pineal organ (Altner, 1965; Vígh-Teichmann et al., 1983b; Vígh-Teichmann and Vígh, 1989; Vígh and Vígh-Teichmann, 1989a). These neurons contain acetylcholinesterase and immuno-reactive glutamate and are endowed with branching dendritic processes that receive ribbon-containing synapses from photoreceptor pinealocytes. The nerve terminals of photoreceptor pinealocytes on their dendrites are glutamatergic. The glutamate-immuno-reactive axons of the secondary neurons run to the habenular nuclei. Neurons of habenular nuclei - receiving retinal afferentation - also send axons to the pineal organ. Small pineal neurons that exhibit GABA-immunoreaction in the cat, send a dendritic process to the pineal recess, and others to the suprapineal recess. A part of the pineal neurons shows tyrosine hydroxylase immunoreactivity. The glutamate- and GABA-immunoreactive CSF-contacting neurons are supposed to be influenced by the parameters of the fluid of the intrapineal and suprapineal recess, respectively. On the basis of the synaptic connections of the GABA-ergic CSF-contacting neurons, they seem to be inhibitory interneurons of the pineal synaptic circuits (Ronnekliev and Kelly, 1984; Ebbesson et al., 1988; Vígh-Teichmann et al., 1991; Vígh and Vígh-Teichmann, 1993, Qu et al., 1994; Vígh et al., 1995a-c; Debreceni et al., 1997; Reuss and Decker, 1997).

Deep encephalic photoreceptors

Several experiments suggested that some CSF-contacting neurons may represent the deep encephalic photoreceptors being sensitive to the illumination of the brain and involved in the photoperiodic regulation (lit. see in: Vígh et al. 2002). Molecules acting in the phototransduction cascade were demonstrated in CSF-contacting neurons of various vertebrates such as in the postoptic commissural nucleus of the lamprey (Foster et al., 1994; Garcia-Fernandez and Foster, 1994), and in the suprachiasmatic, parvi- and magnocellular preoptic nucleus of fish (Kojima et al., 2000; Philp et al., 2000). Concerning amphibians, deep encephalic photoreceptors were identified in the septal, anterior- and magnocellular preoptic, and in the suprachiasmatic nucleus (Yoshikawa et al., 1998; Okano et al., 2000). Most of the results suggest a nonvisual photoreceptive role of these CSF-contacting neurons in the photic control of skin pigmentation or circadian and circannual photoperiodic functions in frogs (Provencio et al., 1998).

In reptiles opsin-containing bipolar CSF-contacting neurons were found in the lateral septum (Hirunagi et al., 1993; Foster et al., 1994). These neurons also immunoreact with VIP (vasoactive intestinal peptide) antibodies (Hirunagi et al., 1995; Grace et al., 1996; Rommel, 1987; Petko and Ihinovien, 1989). VIP-immunoreactive CSF-contacting neurons of the lateral septum were found to form a circumventricular organ-like, circumscribed area ("lateral septal organ") in birds (Kuenzel and Blähser, 1994; Hirunagi et al., 1995). CSF-contacting neurons of the lateral septum showed gene expression of rod/cone phototransduction cascade components (Wada et al., 2000). Axons of opsin and VIP-immunoreactive CSF-contacting neurons of septal and tuberal areas of the avian brain run to the neuropile of the hypothalamus, and constitute a part of the tuberoinfundibular tract projecting to the external layer of the median eminence. VIP fibers were found to innervate GnRh cells in the septal area and deep encephalic photoreceptors were supposed to mediate photoperiodic responses of the gonads in birds (Yamada et al., 1982; Silver et al., 1988; Kiyoshi et al. 1998; Teruyama and Beck, 2001; Saldanha et al., 2001).

5. The medullo-spinal CSF-contacting neurons

The medullo-spinal component of the CSF-contacting neuronal system extends from the distal part of the 4th ventricle to the terminal filum, including the urophysis of fish. Situated around the central canal, the spinal CSF-contacting nerve cells are present from cyclostomes to mammals. Their cytological structure may vary slightly in different species. The average number of spinal CSF-contacting neurons is relatively high in fish and amphibians but they are present in mammals as well. All neuronal elements present in the terminal filum are of CSF-contacting type (lit see: Vígh and Vígh-Teichmann, 1971, 1998; Vígh et al., 1974).

The fine structure of the spinal CSF-contacting neurons does not differ significantly at various segments from the oblongate medulla to the terminal filum. The luminal receptor pole of the CSF-contacting dendrite is supplied with varying numbers of stereocilia being similar to those of known mechanoreceptors like the sensory cells of the inner ear or the lateral line organ of fish and amphibians. The stereocilia contain parallely running filaments and extend radially into the CSF (Fig.

5d). Among the stereocilia there is a long solitary cilium containing microtubuli in an arrangement of 9x2+2-type characteristic of motile kinocilia.

Histochemical and immunocytochemical studies show the presence of several substances in the medullospinal CSF-contacting neurons: AChE, monoamines, urotensin II and somatostatin were demonstrated in these cells in fish. In the rat and mouse GABA, L-amino acid decarboxylase and methionine-enkephalin-Arg6-Gly7-Leu8 imunoreactivity was detected. There are VIP-immunoreacting CSF-contacting neurons in the monkey spinal cord (Barber et al., 1982; Kotrschal et al., 1985; Shimosegawa and coworkers, 1986; LaMotte, 1987; Nagatsu et al., 1988, Yulis and Lederis, 1988; Binor and Heathcote, 2001).

The kinocilia of the neurons were often seen in contact with Reissner's fiber of the subcommissural organ. Reissner's fiber is the condensed secretory product of the subcommissural organ, one of the circumventricular organs. The subcommissural organ situated below the posterior commissure is composed of columnar secretory ependymal cells. Starting from the organ, Reissner's fiber runs through the lumen of the cerebral aqueduct, the 4th ventricle and the central canal (Fig. 5e). According to the early hypothesis of Kolmer (1921), the subcommissural organ, Reissner's fiber, and the receptor neurons around the central canal form a sensory organ, the "Sagittalorgan". This organ was thought to be able to detect motions of the vertebrate column by means of mechanical stimuli caused by the dislocated Reissner's fiber on the sensory processes in the central canal. Some neurophysiological experiments have provided direct evidence of the presence of mechanosensitive neurons intrinsic to the spinal cord in the lamprey (Grillner et al., 1984).

According to another hypothesis, the flow of the CSF in the central canal could dislocate the Reissner's fiber and by this act on the cilia of CSF-contacting neurons similarly to the tectorial membrane of the organ of Corti stimulates the hair cells. In some species, the caudal end of the terminal filum is open and the CSF with the Reissner's fiber flows out of the central canal to the connective tissue spaces surrounding the terminal filum. The outflow of the Reissner's fiber keeps open this terminal hole of the filum (Vígh and Vígh-Teichmann, 1991).

The human subcommissural organ is only active in embryonic life and in the newborn (Leonhardt, 1980). Takeuchi and Takeuchi (1999) found dysplasia of the subcommissural organ in induced hydrocephalus of rats. The question arises as to whether a subcommissural organ that becomes inactive at too early stage may cause a hydrocephalus in humans. Underlining the importance of Reissner's fiber and the opening of the terminal filum, a decreased cerebrospinal fluid flow was found through the central canal of the spinal cord of rats that were immunologically deprived of Reissner's fibre (Cifuentes et al., 1994). There are tight junctions between ependymal cells of the central canal of the urodele Pleurodeles, and the internal CSF does not communicate with intercellular fluid (Zamora and Thiesson, 1980). Therefore, the parameters of the two fluids may be more different in the spinal cord, as compared to those in the brain.

Spinal CSF-contacting neurons are present in the urophysis as well. The urophysis, or neurophysis caudalis of fish - a caudal thickening of the spinal cord - contains large neurosecretory perikarya (Dahlgren-cells) and a zone of neurosecretory terminals similar to the neurohypophysis. The neurosecretory perikarya lying near the central canal send CSF-contacting dendritic terminals into the lumen of the central canal. These dendrites are similar to those of hypothalamic neurosecretory cells and different from the spinal CSF-contacting dendrites (Vígh-Teichmann and Vígh, 1970; Vígh and Vígh-Teichmann, 1973). In the Dahlgren cells a vasodilator and ACTH-releasing neuropeptide urotensin I, the somatostatin-like dodecapeptide urotensin II and, further, a sauvagine-like material were found (Clark et al., 1982; Ichikawa et al., 1982; Renda et al., 1982; Yulis and Lederis, 1988; Larson and Madani, 1991). Some chemical stimuli may be perceived from the inner spinal CSF by the dendrites of the Dahlgren cells lying in the central canal, this information may influence the neurohormonal output of the urophyseal axons.

A similar function was attributed to bioactive substances present in the small medullospinal CSF-contacting neurons. Resembling mechanoreceptors, these neurons may be sensitive to the pressure or flow of the CSF. They send their axons to the outer surface of the spinal cord to form terminals of neurohormonal type. Based on information taken up in the CSF, a regulatory effect on the production or composition of CSF was supposed for the bioactive materials secreted by these terminals (Vígh-Teichmann and Vígh, 1979; Vígh et al., 1983a; Vígh-Teichmann and Vígh, 1989; Vígh and Vígh-Teichmann, 1991, 2002).

6. Axons contacting the external CSF-space

As already mentioned in the preceding chapter, not only the axons of the large neurosecretory cells of the urophysis but also the axons of the small medullo-spinal CSF-contacting neurons run to the external surface of the spinal cord. Using silver impregnation methods, the axons were shown to converge to a bilateral bundle ("centro-superficial tract") and terminate on the ventrolateral surface of the spinal cord. Here, the fibers form neurohormonal nerve endings attached by hemi-desmosomes to the basal lamina of the sipnal cord facing the subarachnoidal space (Fig. 6a). On the surface of the oblongate medulla and spinal cord, these terminals form longitudinal, bilateral neurohemal areas near the ventral roots (Vígh et al., 1977; Vígh-Teichmann and Vígh, 1983).

Most of the axons of hypothalamic magno- and parvocellular neurosecretory nuclei running to

neurohemal areas (neurohypophysis, median eminence terminal lamina, vascular sac) do not termiante on vessels directly, rather, they form neurohormonal nerve terminals attached by hemi-desmosomes to the external basal lamina of the brain tissue (Fig. 6b). Between the basal lamina of the terminals and the basal lamina of vessels there is a space communicating with the subarachnoidal CSF-space. Therefore, similarly to the neurohormonal terminals of the medullospinal CSF-contacting neurons, they represent external CSF-contacting axon terminals. The bioactive materials released from these endings primarily enter the external

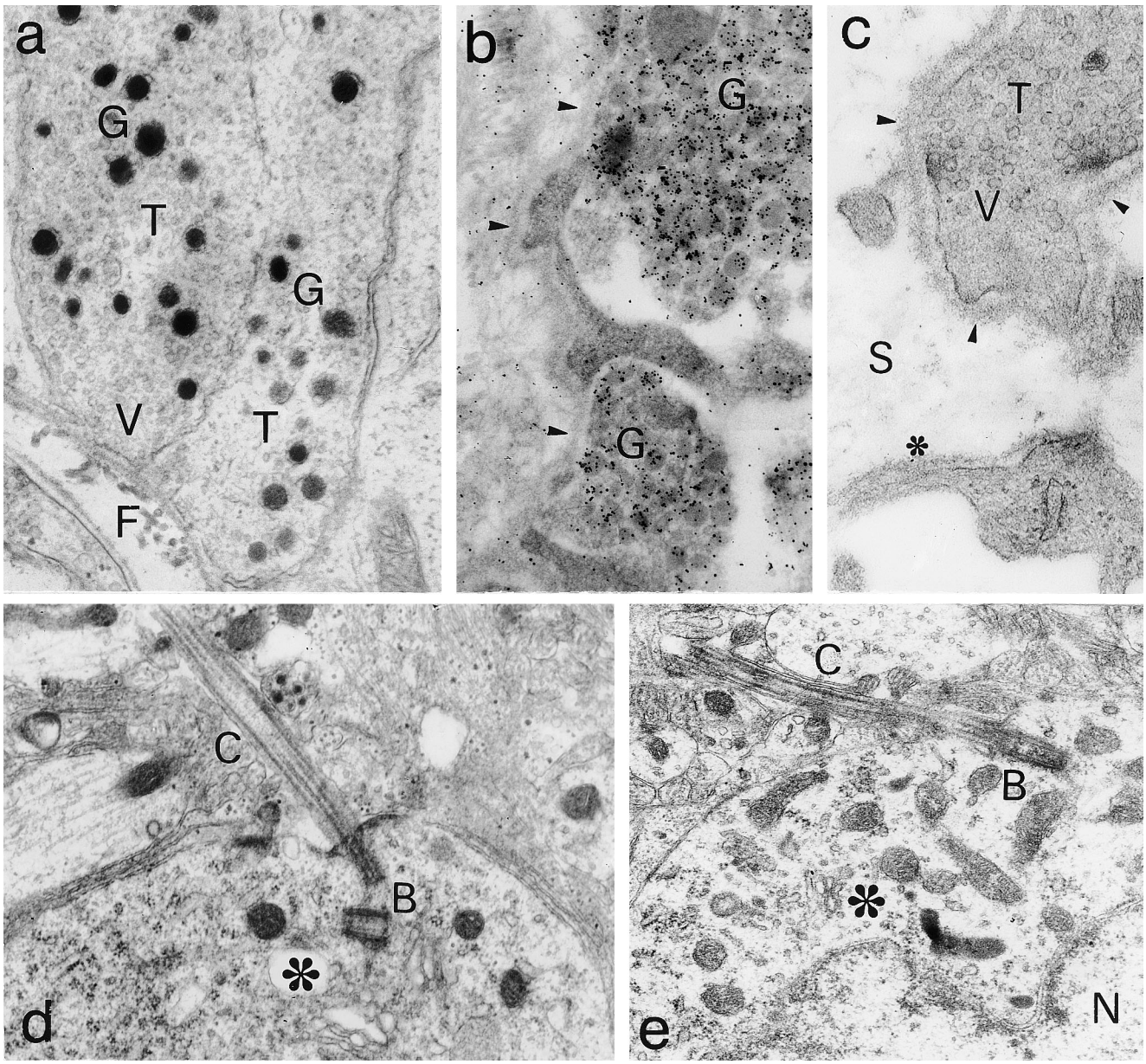

Fig. 6. a. Neurohormonal terminals (T) formed by the axons of medullo-spinal CSF-contacting neurons on the subarachnoidal surface of the spinal cord in the lamprey, F: collagenous fibers, G: granular vesicles, V: synaptic vesicles. x 25,500. **b.** Neurohormonal axon terminal facing the basal lamina (arrow-heads) of the vascular surface of the neurohypophysis of the turtle *Pseudemys scripta elegan*s. Neurophysin immunoreaction (black dots of immunogold particles) on granular vesicles (G), x 66,000. **c.** Neurohormonal terminal (T) on the basal lamina (arrow-heads) of the subarachnoidal space (S) of the pineal organ of the chicken, asterisk: basal lamina of the vessel, V: accumulation of synaptic vesicles. x 48,000. **d.** Intercellular cilium (C) of a neuronal perikaryon (asterisk) of the parvicellular preoptic nucleus of the lizard (Lacerta agilis). B: basal bodies. x 21,600. **e.** Cilium (C) of a neuron protrudes into the intercellular space in the Guinea pig posterior hypothalamus. B: basal body, N: nucleus. x 20,800

CSF and secondarily - by diffusion - into vessels. A modulatory effect of the external CSF on the hormones secreted cannot be excluded.

Similar neurohormonal terminals were found in the pineal organ (Fig. 6c). The effector pole of pinealocytes is represented by an axonal process that terminates either on secondary pineal neurons, or forms neurohormonal nerve terminals (Manzano e Silva et al., 1996). The neurohormonal endings terminate on the basal lamina of the vascular/superficial surface of the pineal tissue. The capsule and septa of the pineal organ are formed by arachnoidal and pial sheaths of the diencephalon. Therefore, these neurohormonal terminals contact the external CSF space present in the pineal arachnoid. The terminals of pinealocytic processes presumably secrete melatonin, the hormonal substance of the organ. We found serotonin immunoreaction localized on the granular vesicles that fill the superficial neurohormonal terminals in the pigeon (Vígh and Vígh-Teichmann, 1989a). Immunoreactive aspartate and especially glutamate were also found to accumulate in the neurohormonal terminals on the surface. A role of excitatory amino acids in the hormonal efferentation of the pineal organ - similar to its role in the neurohypophyseal hormonal release - was put forward (Meeker et al., 1991; Vígh et al., 1995a,b; Vígh and Vígh-Teichmann, 1998).

7. Ciliated neuronal perikarya contacting the CSF and intercellular fluid

In most nuclei of the periventricular gray of the hypothalamus in reptiles and birds, the perikarya lying farther away from the ependyma do not send dendrites into the ventricles, but have a 9+0-type cilium extending into the intercellular space (Fig. 6d, e). As we have seen concerning the neurosecretory cells, ventricular dendrites of subepedndymal cells were supposed to serve as osmoreceptors for these nuclei (Dierickx, 1962; Korf et al., 1982). The cilia on distal perikarya were found in magnocellular and parvicellular nuclei es well. Contacting the intercellular space, these ciliated perikarya were supposed to detect parameters of the intercercellular fluid (Scharrer, 1966; Vígh-Teichmann et al., 1970b, 1976a,b; Vígh-Teichmann and Vígh, 1983). It may also be supposed that the cells of the same nucleus having intraventricular dendrites modulate their activity according to the composition of the ventricular CSF and the distal ones according to the intercellular fluid. Finally, the connection found between both neurons may serve for the detection of differences between the two fluids.

In mammals most of the perikarya in the hypothalamic periventricular gray have a cilium, those lying subependymally, as well as those being farther away from the ventricle (Vígh-Teichmann and Vígh, 1983; Vígh and Vígh-Teichmann, 1998). The subependymal perikarya were supposed to derive from the CSF-contacting neurons of lower vertebrates. Since in the hypothalamus (but not in the spinal cord: Zamora and Thiesson, 1980) the ependymal cells are connected by permeable zonulae adherentes and it seems likely that the composition of the intercellular fluid around the subependymal neurons changes parallel to that of the CSF. Therefefore, they may function similarly to those sending dendrites into the CSF of submammalians (Vígh-Teichmann et al., 1976a,b, 1980b). As in prochordetes all neurons lie around the lumen of the central nervous system and send a ciliated dendrite into them, also the distal neurons of the phylogenetically more developed brain seem to derive from CSF-contacting neurons (Vígh-Teichmann et al., 1980c; Vígh and Vígh-Teichmann, 1982a,b, 1998; Vígh-Teichmann and Vígh, 1983, see also in General conclusions).

General conclusions

Several investigations confirm the importance of nonsynaptic signal tranmission in the function of the nervous tissue (Florey, 1984; Otellin, 1987; Buma, 1988-1989; Vizi, 1990, 2000, Bach-y-Rita, 1993; Golding, 1994; Jefferys, 1995; Freund, 2002). Present in various periventricular brain regions of vertebrates, the various CSF-contacting neurons (Fig. 7) seem to have a special role in taking up, transforming and emitting nonsynaptic signals mediated by the internal and external CSF in connection with the intercellular fluid of the brain (MacDonnell, 1983; Frank et al. 2002). Further, the comparative histology of the CSF-contacting neurons of various vertebrates presented in this review furnish new insight into the possible evolution - and by this a better understanding of the importance - of the inner and outer fluid environment of the brain tissue.

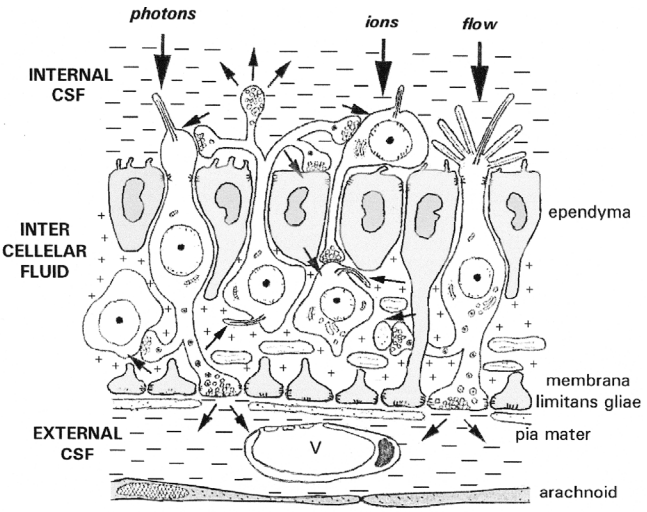

Fig. 7. Scheme of the various CSF-contacting neuronal elements and their relation to the inner or outer CSF and intercellular space. The arrows indicate nonsynaptic, synaptic and neurohormonal signal transduction. V: vessel.

As we have seen in the relevant chapters, more neurons were found to form dendritic terminals in the ventricles of lower vertebrates than in more differentiated species. Looking for an explanation of this phenomenon in the phylogeny of the brain, we also investigated the central nervous system of animals of the deuterostomian line of evolution, namely, the echinoderm starfish (*Pisaster ochraceus*, *Asterina gibbosa*, *Holothuria forskali*), that exhibit a neural plate-like nervous system. In these animals, dendrite-like processes of the nerve cells of the ectoneural radial cord were found terminating with ciliated bulb-like endings below the cuticle that faces the sea water. The cilia are of the sensory type, containing 9x2+0 tubuli, like those of the CSF-contacting neurons of vertebrates. These dendrite terminals were supposed to have some significance in perceiving the actual composition or physical parameters of the sea water and accordingly to modulate the activity of the nervous system (Vígh and Vígh-Teichmann, 1982a,b, 1991).

In the more differentiated chordate lancelet (*Branchiostoma lanceolatum*) nearly all neurons were found to be in direct contact with the CSF in the neural tube-like central nervous system. The sea water still enters the ventricular lumen of the "brain" through the open anterior neuroporus of the larval lancelet and represents the first "internal" fluid environment of the brain tissue. The direct contact of larval neurons with the sea water is modified in adults in which the neuroporus is already closed and the cells establish a contact with the modified sea water: the primary cerebrospinal fluid. The composition of this new fluid depends no more directly on the environment, but on the activity and metabolism of the brain; therefore, we expect a basic regulatory function of the CSF-contacting neurons in connection with the metabolic state of the brain tissue (Vígh and Vígh-Teichmann, 1982b, 1998; Vígh-Teichmann and Vígh, 1983). Since in the lancelet, nearly all neurons contact the lumen of the central nervous system, it was believed that the CSF-contacting neurons of vertebrates are derived from an ancient epithelial neuron-type of the ectoderm, and thereby represent a phylogenetically old cell type, the "protoneuron" (Vígh and Vígh-Teichmann, 1982a). During evolution, the more differentiated neurons of vertebrates migrated away from the ventricle and their cilia extended into the intercellular fluid gaining significance in nonsynaptic exchange of information in higher vertebrates (Fig. 8).

Remaining in contact with the ventricular sytem of various vertebrates, the dendritic CSF-contacting neurons are present in special periventricular nuclei and ependymal organs. Not yet found in lower vertebrates, the telencephalic CSF-contacting dendritic areas appear in reptiles and birds in which the other CSF-contacting dendrites of mostly hypothalamic areas become reduced. In mammals, only the CSF-contacting neurons of the spinal cord retained their ancient structure. The CSF-contacting neurons present among secondary neurons of the retina are the Landolt bipolars and the secondary neurons of the pineal organ. Retinal and pineal photoreceptors themselves develop from bipolar neuroblasts in the wall of the optic ventricle and pineal recess, respectively. Therefore, they seem to belong to the same cell type as CSF-contacting-like neurons. Retina, pineal organ and hypothalamic CSF-contacting neurons are all parts of the diencephalon that can be regarded as the predominantly visual part, the "photo-encephalon" of the brain (Vígh and Vígh-Teichmann, 1973, 1975, 1988, 1999). The genetical similarity of these cells is emphasized by the finding that the regenerating retina of newt photoreceptors develop from Landolt bipolars. In experimental conditions supposed infundibular CSF-contacting neurons develop photoreceptor outer segments (Sacerdote, 1971; Grigorian, 1996)

The comparative aspects of the axons contacting the external CSF show that the axon terminals of neurohormonal-type - like those of the median eminence and neurohypophysis - also represent a phylogenetically old form of nonsynaptic transmission of information. Namely, the above mentioned lancelet does not possess somatomotoric nerves at all, but the axons of corresponding motoneurons run to the ventral surface of the central nervous system and form terminals of neurohormonal-type there. Processes of the myotoms are extended to this area from outside and take up the information secreted by these terminals. A spinal CSF-contacting neuron of higher vertebrates sending its axon to the outer surface of the spinal cord represents on its receptor as well as effector pole the phylogenetically oldest structure in the brain for uptake and release of information: the CSF-contacting dendrite and the neurohormonal axon ending. If a neuronal form is functioning for about 600 million years (the estimated age of lancelets) we should consider it as an important structure in the basic functions of the central nervous system.

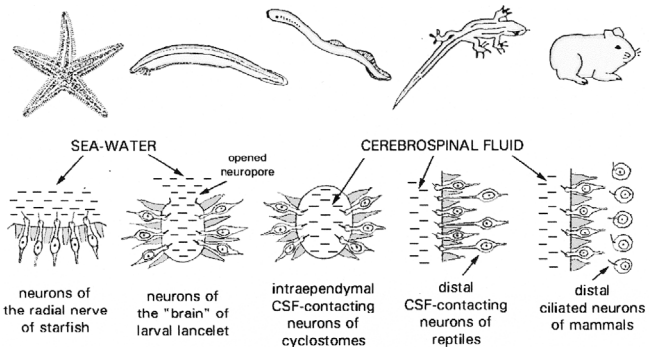

Fig. 8. Scheme on the supposed evolution of the cerebrospinal fluid, CSF-contacting neurons and ciliated neuronal perikarya of vertebrates.

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