# The Circumventricular Organs of the Brain: Do They Represent a Cerebrospinal Fluid-Dependent Regulatory System?

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**Abstract.** The circumventricular organs are specially organized areas in the wall of the brain ventricles. The close contact of their cells to the internal and external cerebrospinal fluid (CSF) spaces supports the hypothesis that their function is connected to the maintenance of the homeostasis of these fluids. The neurons of the subfornical organ, and area postrema send receptor dendrites to the perivascular surface of the nervous tissue and may perceive the composition of the perivasal fluid. Some of the circumventricular organs form neurohormonal release areas similar to those of the neurohypophysis, the lack of blood-brain barrier in these areas primarily serves the hormone release. The CSF-contacting neurons of the paraventricular organ form dendritic terminals in the third ventricle and are supposed to be chemoreceptors. Similar neurons in the lateral septal organ and preoptic recess of submammalians contain opsins and represent the deep brain photoreceptors detecting the illumination of the CSF and influence photoperiodicity. CSF-contacting neurons around the central canal show cytologic similarity to known mechanoreceptors and are supposed to perceive the flow or pressure of the CSF. Neurons sending a sensory cilium into the intercellular space may perceive the chemical composition of the intercellular fluid that is important in the metabolism and non-synaptic signal transmission of the brain. The subcommisural organ contains special ependymal cells secreting the Reissner's fiber which extends into the mesencephalic aqueduct, fourth ventricle and central canal. The fiber may help the supposed mechanoreceptive task of the spinal CSF-contacting neurons and seems to be involved in the pathogenesis of hydrocephalus.

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1. INTRODUCTION

The circumventricular or periventricular system is formed by organ-like areas around the brain ventricles. Being dissimilar to the general structure of the ventricular wall, they are composed by special neurons, ependymal and glial cells. In 1942 Legait [1] was the first summarising data on three periventricular organs: the subcommissural organ, paraventricular organ and subfornical organ and in 1958 Hofer [2] named these and similar areas circumventricular organs. The first symposium on the circumventricular organs and cerebrospinal fluid was organized in 1969. In an early review, in 1971, we summarized data available on the subcommissural organ, paraventricular organ, subfornical organ, area postrema, organon vasculosum laminae terminalis, saccus vasculosus, parapophysis, recessus infundibuli- and recessus preopticus organ. They were grouped in ependymal, hypendymal and choroid organs [3]. Later similar structures were described in other ventricular areas like the nuclei of CSF-contacting neurons sending a dendrite to the ventricles or the urophysis spinalis a caudal neurosecretory area, further, in a wide sense the median eminence, neurohypophysis, choroid plexuses and pineal organs were also listed among circumventricular organs [4,5].

Some of these ventricular areas like the vascular organ of the terminal lamina, median eminence, neurohypophysis, urophysis, medullospinal CSF-contacting neurons and some pineal areas contain nerve fibers forming neurohormonal release sites, where axon terminals pierce the external glial limiting membrane of the nervous tissue and contact directly the perivasal spaces to release there neurohormones, consequently, at these areas the blood-brain barrier is lacking. On the basis of experimental works, these hormone releasing effector areas of the brain were generally considered as receptor zones for bioactive substances circulating in the blood [6-7].

For further improvement of hypotheses about the functioning of circumventricular organs, in the present paper, giving a complete review of all special circumventricular structures (FIGURE 1), we focus on their relation to the ventricular and subarachnoidal CSF and intercellular fluid of the nervous tissue. Also considering their fine structure and neurohistological organization and comparative morphophysiology in various vertebrates and human, in the followings we discuss the circumventricular organs according to their ventricular location.

1. Lateral ventricle and rostral, medial-telencephalic part of the 3rd ventricle: lateral septal organ, preoptic recess organ, subfornical organ and organon vasculosum laminae terminalis.

2. Diencephalic part of the 3rd ventricle: paraventricular organ and CSF-contacting neuronal areas, vascular sac, parapophysis, dorsal sac and pineal organs.


2. THE LATERAL VENTRICLE AND TELENCEPHALON MEDIUM

A. LATERAL SEPTAL AND PREOPTIC RECESS ORGAN

"Lateral septal organ" was called an area formed by special CSF-contacting neurons sending dendrites to the ventricular lumen of the septum of birds [8]. In the preoptic area (developmentally considered to represent the telencephalon medium in contrast to the hemispheres representing the telencephalon laterale) there are monoaminergic CSF-contacting neurons (FIGURE 2) in amphibians around the preoptic recess ("preoptic recess organ") that belongs to the rostral part of the parvicellular preoptic area [9]. Molecules acting in the phototransduction cascade were demonstrated in these septal, further in the anterior- and magnocellular preoptic, and suprachiasmatic nuclei of submammals. Several experiments suggest that these opsin-containing CSF-contacting neurons may represent the deep encephalic photoreceptors, their intraventricular dendrites and 9+0-type cilia correspond to the inner and outer segment of photoreceptor pinealocytes or retinal cones and rods. Being sensitive to the illumination of the CSF, they are involved in the photoperiodic regulation of birds and heat-regulation of cold-blooded species [10].
In lampreys, immunoreactive rod and cone opsins, alpha-transducin and arrestin were found in CSF-contacting neurons of the preoptic nucleus, postoptic commissural nucleus and in the ventral and dorsal hypothalamic nuclei. It was supposed that in cyclostomes these different populations of encephalic photoreceptors individually influence various brain centers involved in control of periodic functions [11].

In fishes, a newly recognized opsin VA (vertebrate ancient) was localized in preoptic and suprachiasmatic nuclei acting in skin colour regulation in relation to environmental light conditions [12]. In amphibian rhodopsin, rod- and cone transducin-immunoreactive CSF-contacting neurons were found in preoptic and suprachiasmatic nuclei. Septal and preoptic CSF-contacting neurons reacted with antibodies against toad retinal rhodopsin. The axons of these neurons could be traced to the periventricular neuropile and into the neural lobe and pars intermedia of the pituitary, a connection suggesting the control of release of melanocyte-stimulating hormone of the pars intermedia by preoptic recess organ [13].

In reptiles, bipolar CSF-contacting neurons of the lateral septum immunoreacting with VIP (vasoactive intestinal peptide)-antibodies also show gene expression of rod/cone phototransduction cascade components. These neurons send axons to the neuropile of the hypothalamus, and to the
VIP fibers innervate GnRH cells in the septal area in birds and deep encephalic photoreceptors were supposed to mediate photoperiodic responses of the gonads [14,15].

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 [16]. Encephalopsin, a putative deep brain opsin was detected in the mammalian preoptic area and paraventricular nucleus as well [17].

**B. SUBFORNICAL ORGAN**

The organ is well developed in mammals and human [18]. Lacking a fornix similar to that of mammals, the homologous organs in submammalian are also called subseptal or interventricular organ. In the frog, neurons of the organ send CSF-contacting dendrites to the CSF where they form bulbous intraventricular terminals bearing a 9+0-type sensory cilium [19]. The ventricular dendrite may be sensitive to the composition of the CSF.

Corticotropin-releasing hormone-like immunoreactive neurons are present in the reptilian subfornical organ [20]. The organization and fiber connections of the avian subfornical organ were found to be similar to those of mammals. Angiotensin II has an activating effect on subfornical organ neurons of the duck [21]. In pigeons, the subfornical organ was found to be necessary for thirst evoked by intraperitoneally administered angiotensin II [22].

In mammals, the subfornical organ is sitting at the transitional zone of corpus fornici and columnae fornici in association with the hippocampal commissure (FIGURE 3). Branches of the anterior cerebellar artery reach the organ form the
The circumventricular organs of the brain are connected to the choroid plexus and form a capillary network showing endothelial fenestrations. There is a broad connective tissue layer containing autonomic nerve fibers around the vessels. The veins enter the internal cerebral veins. Intravenously administered vital stain appears in the organ due to the lack of blood-brain barrier. The organ develops from the commissural plate and is completing its development relatively late in the postembryonic time [19, 23]. A tumor found in the human left ventricle showed characteristic structures of the subfornical organ [24].

There are several small and some larger, multipolar neurons in the organ. Subependymal neurons can be found to be very close to the ventricle separated from it by a thin ependymal cytoplasm only. Dendrites of small neurons penetrate the basal lamina and protrude into the perivasal space and their axons form synaptic contacts with dendrites of the large multipolar neurons. The axons of the latter form myelinated efferent projections. Afferent fibers terminate on both the small and large neurons [19, 25]. The efferent fibers have large projections to the paraventricular and supraoptic nuclei and to the lateral area of the hypothalamus as well as to limbic and basal forebrain structures. Electrical stimulation of the SFO activates septal (LHRH) neurons projecting to median eminence [26, 27]. Afferent fibers connect the organ with the cardiovascular responsive region of the caudal ventrolateral medullary depressor sites. Fibers are also coming from the dorsal raphe nucleus, nucleus of the solitary tract and arcuate nucleus. The parabrachial nucleus sends a substantial projection to the subfornical organ. Ascending projections of the nucleus tractus solitarius to the subfornical organ decreases noradrenaline release of the organ. Septal cholinergic afferent pathways are activated under hypovolemic conditions [28, 29].

Due to the lack of blood-brain barrier in the subfornical organ, their neurons are generally regarded as sensory elements monitoring changes in osmotic, ionic and hormonal composition of the...
blood [30,31]. Neurocytologically, the dendrites of neurons crossing the limiting membrane of the glial feet and penetrating the perivasal space may represent these receptors. As we have seen above, neurons also send dendrites between ependymal cells into the ventricular lumen, and experimental data also have shown that subfornical neurons are influenced by ventricular CSF [23]. Administration of angiotensin II to the lateral ventricle and to the subfornical organ induces drinking [33]. Endothelin-1, a vascular- and brain-derived constricting peptide, infused intraventricularly caused hypermetabolic responses in the subfornical organ, but it is without effect when administered intravenously [32]. Angiotensin II receptor content in hydrocephalic animals increases in the subfornical organ [34]. Indicating a role in the detection of central energy substrate availability, intracerebroventricular administration of SGLT1 Na+-D-glucose cotransporter inhibitor resulted in induction of ependymal glial and neuronal transactivation in the subfornical organ [35]. Central and peripheral infusion of angiotensin II strengthen the view that there are independent receptor systems subserving the dipsogenic responses to peripheral and central administration [36].

C. ORGANON VASCULOSUM LAMINAE TERMINALIS (OVLT)

Present from fishes up to mammals, the OVLT is situated below the anterior commissure in the ventral part of the anterior wall of the third ventricle (FIGURE 4). It is composed by small neurons, glial cells and numerous vessels and has an affinity to vital stains and horseradish peroxidase injected intravenously [37,38]. Neurohistologically, the most characteristic structure of the OVLT is the neurohaemal area formed by several axons terminating with neurohormonal endings on the vascular surface of the neural tissue in a manner similar to what is known in the median eminence or neurohypophysis [39]. The nerve cells of the organ contain immunoreactive corticotropin-, and thyrotropin-releasing factor in fishes [40]. Luteinizing hormone-releasing hormone-immunoreactive fibers penetrate the ependymal lining and may release this neuropeptide into the CSF [42]. Afferent fibers to the organ are coming from the hypothalamic parvicellular paraventricular nuclei in the rat [43] and somatostatin-immunoreactive fibers were demonstrated to reach the area in the trout [44]. Efferent fibers of the OVLT were traced to the avian paraventricular nucleus [45] and neurons displaying hypophyseal connections were identified in this area of the catfish [46]. The efferent neural pathways to the hypothalamic paraventricular and supraoptic nuclei mediate vasopressin secretion in response to plasma hypertonicity and increased circulating levels of angiotensin II. Neurons in the lamina terminalis have efferent polysynaptic connections to the peripheral sympathetic nervous system as well, and may exert an inhibitory osmoregulatory influence on renin secretion by the kidney. The OVLT also exerts an osmoregulatory influence on renal sodium excretion that is independent from the renal nerves and seems to be hormonally mediated [47,48].

Experimental works generally consider the neurohaemal zone of the effector neurosecretory axon terminals without blood-brain barrier as the morphological basis of the receptory functions of the organ that are associated with cardiovascular and body fluid regulation [31]. The organ mediates thirst, sodium appetite and vasopressin release not only in response to intravenous infusion but also after intracerebroventricular administration of angiotensin [49,50]. Intracerebrovascular administration of cholinergic receptor agonist activates lamina terminalis neurons projecting to the supraoptic nucleus and induces water intake, vasopressin release and increase of arterial blood pressure [51]. OVLT and choroid plexus activity was found during increased water and sodium intake caused by partial aortic ligature [52]. The organ is a possible access point for circulating pirogens to cause fever [53]. Further, direct injections of lactate into the OVLT elicits anxiety-like responses with chronic dysfunction of GABA neurotransmission in the dorsomedial hypothalamus [54].
3. THE DIENCEPHALIC PART OF THE THIRD VENTRICLE

A. PARAVENTRICULAR ORGAN

Formed by a special columnar ependyma and two neuronal layers, the paraventricular organ is a bilateral structure in the hypothalamus. Some of the neurons are bipolar and sit intra- and subependymally, others are multipolar and form a distal group, both sending ciliated CSF-contacting dendritic terminals into the 3rd ventricle (FIGURE 5). Intraventricular axons terminate by axodendritic synapses on these dendrites. The arborization pattern of the monoamine-containing axons of the hypendymal neurons show that they terminate not only around the distal perikarya but also in the fibrous synaptic zone of the lateral hypothalamus [55,56]. Intraependymal perikarya also form somatodendritic synapses showing the receptor character of these cells [57].

Several fiber tracts originate from the organ. In the chicken, there is an AChE-positive fiber bundle going to the thalamus. Monoamine-containing fibers of the organ were found to terminate in the median eminence. Furthermore, axons were traced to isodendritic neurons of the lateral hypothalamus. Ascending projections to hypothalamic and extrahypothalamic areas are particularly well developed in the lungfish [58]. Major targets include the dorsal hypothalamus, the periventricular preoptic nuclei, the habenula, the subhabenular region, the anterodorsal thalamus and telencephalic septum. Most of the ascending fibers follow the medial forebrain bundle while 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 as well, further in the proximal pars distalis and in the neurointermediate lobe of the goldfish [59]. Degeneration experiments in the newt established the existence of a fiber projection to the striatum. Experimental lesions of the organ resulted in alteration of motoric behavior [60].

Various bioactive compounds were demonstrated in the neurons of the organ, like noradrenaline, dopamine, L-dopa, 5-hydroxytryptamine, tyrosine hydroxylase, neuropeptide Y, vasoactive intestinal protein, substance P, somatostatin, nitric oxide synthase, GABA and galanin [61,62]. Immunolocalization of catecholamine enzymes (dopamine- and tyrosine-hydroxilase) has also been reported in the CSF-contacting neurons. Other authors failed to detect these synthesizing enzymes and discuss the possible role of the organ in the intraventricular uptake and/or transport of biogenic amines [63,64,65]. Corticotropin releasing factor-immunoreactive neurons were demonstrated in the snake paraventricular organ [66].

Administration of CaCl₂, NaCl, and NaHCO₃ into the lateral ventricle of chickens and sparrows resulted in an increase of induced monoamine fluorescence in the organ. 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 [16,67].

The posterior recess in the fish mamillary region may represent the caudal continuation of the paraventricular organ. In the folded posterior recess of cartilaginous fishes a high number of aminergic CSF-contacting neurons are present, they contain monoamines and neuropeptide-Y and their axons terminate in the neuropile of the hypothalamus [68,69,70]. CSF-contacting neurons of this nucleus retrogradely labeled with cobaltous lysine were found to project into the pituitary stalk of catfish [46]. LHRH-immunoreactive fibers organizing reproductive behaviors terminate in the medial posterior tuber [71]. Bipolar serotonin immunoreactive CSF-contacting neurons are also present in the caudalmost wall of the third ventricle in birds, with localization similar to that of the nucleus of the posterior recess of fishes [72].
The wavy paraventricular ependyma of the third ventricle of mammals is regarded as homologue to the paraventricular organ of submammals. This ependymal area is not uniformly developed in the various mammals studied. It contains subependymal nerve cells in the cat, in the insectivorous hedgehog and marsupial opossum. In the hedgehog some of the intraependymal neuronal perikarya contact the CSF and may correspond to the CSF-contacting neurons of submammalian vertebrates [16,73]. An equivalent of the paraventricular organ was reported to have been identified in the human fetus as well [74].

**B. CSF-CONTACTING NEURONAL ELEMENTS**

There are different types of CSF-contacting neuronal elements: dendrites, perikarya and axons may enter the ventricular CSF and also may contact the external CSF-space. Neurons sending ciliated dendrites to the ventricle (Figure 6) were supposed to be CSF-receptors. They are present not only in the paraventricular, preoptic and lateral recess organ but in several magnocellular and parvicellular nuclei of the hypothalamus of submammals. In mammals the arcuate nucleus send dendrites to the infundibular recess and intraependymal neurons around the central canal contact the CSF [16,75].

Supraependymal neurons were found from cyclostomes to mammals at various sites of the ventricles, e.g., in the mesencephalon of cartilaginous fishes in the so-called mesencephalic midline ridge formation. In mammals there are several neuronal perikarya in the infundibular and mamillary recesses or above the area postrema or lateral aperture of the 4th ventricle [76]. The axons of these nerve cells cross the ependymal lining and enter the periventricular synaptic zone.

Several perikarya of the mammalian periventricular gray have a 9+0-type cilium, some of them sit subependymally, others farther away from the ventricle. The subependymal perikarya are supposed to function like the CSF-contacting neurons of lower vertebrates, because there are gap junctions between ventricular ependymal cells.
permitting the mixing of CSF and intercellular fluid around the subependymal neurons. In contrast, in the spinal cord, tight junctions are separating the two fluid spaces [77], therefore, ciliated spinal neurons (FIGURE 7) may be dependent from the intercellular fluid only being important in the nonsynaptic signal transmission of the nervous tissue [78,79]. A similar communication may be supposed between external CSF and intercellular fluid across arachnoid matter [80].

Intraventricular axons are present in the highest number in mammals. Supraependymal nerve fibers were found in the human brain as well [81]. Some of these fibers form synaptic contacts on intraventricular dendrites and neuronal perikarya, or innervate the luminal surface of the ependyma (FIGURE 8). Another type of intraventricular axons terminate in 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 they may release hormones into the CSF [16].

Axons contacting the external perivascular or CSF-space are neurosecretory fibers like those of the OVLT, meadian eminence, neurohypophysis or urophysis. They do not terminate directly on vessels as generally believed, rather, they form neurohormonal nerve terminals attached by half-desmosomes to the external basal lamina of the brain tissue. Between the basal lamina of the perivascular nervous tissue and the basal lamina of vessels there is a space communicating with the subarachnoidal CSF by the Virchow-Robin spaces. Regarding this relation, the neurosecretory terminals represent external CSF-contacting axon terminals. The hormones released from these endings primarily enter the fluid of the perivascular space and secondarily, by diffusion, into vessels. The external CSF may have a modulatory effect on the bioactive materials secreted by these endings [79,80].
C. SACCUS VASCULOSUS

Present in various fish species, the vascular sac evaginates from the dorsal wall of the infundibulum and forms several epithelial pouches surrounded by vessels. The blood flow of the sinusoid vessels is regulated in some cartilaginous fish by perivasal rings of smooth muscle cells. The epithelium of the organ is formed by ependymal cells, among them the so-called coronet cells and some CSF-contacting neurons are sitting. The lumina of the organ are filled by the ventricular CSF [56,82].

The CSF-contacting neurons of the vascular sac show immunoreactivity for serotonin, neuropeptide Y, gamma-aminobutyric acid and glutamic acid decarboxylase. Their axons contribute to the fibers of the nervus sacci vasculosi going to the nucleus (ganglion) sacci vasculosi and to the ventral thalamus [82,83]. A sacco-thalamic fiber tract runs rostrally to the nucleus sacci vasculosi and splits into two branches that reach the subhabenulo-preoptic region. GABA, NPY, and glutamic acid decarboxilase as well as immunoreactive parathyroid hormone-related peptide and its receptors were detected in the neurons of nucleus sacci vasculosi. Afferent LHRH-immunoreacting fibers acting in reproductive behaviors terminate on its neurons. In some nerve fibers of the organ, immunoreactive neuropeptide Y and thyrotropin-releasing hormone was demonstrated [84-87]. Indicating a neurosecretory activity, the basal axonal process of the CSF-contacting neurons filled with large granular vesicles form neurohormonal terminals at the vascular surface of the organ in the ray [56].

The coronet cells (Figure 9) have a luminal process bearing several bulb-like cilia filled with parallely arranged tubular cisternae. The ultrastructure of the perikarya is characterized by abundance of smooth endoplasmic reticulum showing immunoreaction for parathyroid hormone-related protein [88,89]. There are afferent axosomatic synapses on the basal part of the coronet cells [82]. The neuronal character of the coronet cells is still under debate since an efferent axon or synapse formed by the cells has not yet been demonstrated. Earlier authors considered the coronet cells as mechanoreceptors that would detect the depth of water in fishes [90]. The coronet cells may also be involved in transcellular ion transport for the CSF [91]. Calcium-sensitive receptors were demonstrated in the coronet cells by in situ hybridization [92].

D. PARAPHYSIS AND SACCUS DORSALIS

The paraphysis (Figure 10) forms several saccular evaginations of epithelial character on the top of the third ventricle caudal to the choroid plexus. Present in lower vertebrates, and in embryos of higher vertebrates, it is well developed in amphibians and reptiles [93]. The organ is similar to the choroid plexus, but in contrast to protruding intraventricularly, the paraphysis is an extraventricular saccular evagination. It contains a dense capillary plexus, its cuboid-cylindrical epithelium is secreting a glycoprotein [94]. Epithelial cells of both the paraphysis and choroid plexus exhibit similar ultrastructural features: a well developed microvillar border and apically located mitochondria, which indicate an active exchange between the blood and CSF [95]. An intense Ca++-ATPase activity demonstrated on the plasmalemma of the microvilli indicate a Ca++-ion regulation for the CSF [96]. Also the occurrence of bone fractures and parathyroid hyperplasia in parathyroidectomised frogs speaks in favor of a role in calcium metabolism for the organ [97]. It was discussed whether rudiments of the paraphysis in higher vertebrates and human may develop cyst or tumors [98,99].

The dorsal sac (saccus dorsalis, parencephalon) is another choroid plexus-like epithelial organ forming a solitary evagination between paraphysis and pineal organs. In some animals (e.g., Elaphantopus planiceps) it is well developed, in mammals it forms the suprapineal recess [100]. Arginine vasotocin and isotocin immunoreactive nerve fibers were found to innervate the dorsal sac [101]. Various enzymes demonstrating a high metabolic activity were found in the organ [102]. Ependymins (exoglycoproteins) being present in the choroid plexus were also found in the meningeal layer of the dorsal sac [103]. Saccus dorsalis — similarly to the choroid plexus and the hypothalamic vascular sac — seems to be a frequent route by which the central nervous system may become haematogenously infected by bacteria [104].
In some cyclostomes lacking choroid plexus, the dorsal ependymal region of the central canal forms a separate lumen lined by special ependyma (Figure 11), that may produce or exchange components of CSF [105,106].

E. PINEAL ORGANS

Measuring the light intensity of the environment, the pineal organs of submammalian vertebrates contain photoreceptive pinealocytes. They have well developed outer segments containing cone- and rod-type opsins, or the pineal specific pinopsin. Similar to retinal photoreceptors, some of the pinealocytes of birds express chryptochrome-1 demonstrated by immunocytochemistry and in situ hybridization. Chryptochrome is a blue light sensitive molecule which also may participate in the circadian clock-mechanism of the organ. In mammals the photoreceptor outer segment of pinealocytes is represented by a simple sensory cilium of 9x2+0-type. In young ferrets, the cilia develop outer-segment-like structures and in some mammals immunoreactive opsins were found in the cell membrane of pinealocytes, but the mammalian pineal is generally considered as a light-insensitive organ [107-109].

There are secondary neurons in the pineal as the main elements of neural efferentation of the organ. Axon-like processes of pinealocytes form axodendritic synapses on their dendrites and the axons of these neurons run to different brain stem areas, first of all to habenular nuclei. Both the axon terminals of pinealocytes and the secondary neurons accumulate immunoreacting glutamate and aspartate. In addition, matabotropic glutamate receptors were demonstrated postsynaptically showing the glutamatergic character of the pinealofugal pathways. Glial glutamate transporter GLT-1 responsible for the removal of glutamate from the extracellular fluid of the brain tissue is expressed in the pineal organ [109,110].

In the cat, small pineal neurons that exhibit GABA-immunoreaction, send dendritic processes to CSF of the pineal recess, and others to that of the suprapineal recess being the derivative of dorsal sac of lower vertebrates. These glutamate- and GABA-immunoreactive CSF-contacting neurons are supposed to be influenced by the parameters of the fluid of the intrapineal and suprapineal recess [108,111].

Axonal processes of pinealocytes also form neurohormonal terminals on the vascular surface of
the pineal organ (Figure 12) and are thought to represent the release sites of hormones produced in the organ. As serotonin was localised in the granular vesicles of the neurohormonal terminals, we suppose they serve the release of that molecule, as melatonin produced in pinealocytes may cross the cell membrane without specific release organelles. Pinealocytes protruding into the suprapineal and the intrapineal recess were supposed to release melatonin into the internal CSF and by this directly acting on the periventricular organs and subependymal neurons of the brain [109,112,113].

3. MESENCEPHALIC AQUEDUCT, 4TH VENTRICLE AND CENTRAL CANAL

A. SUBCOMMISSURAL ORGAN

Located at the transitional zone between the third ventricle and mesencephalic aqueduct, the subcommissural organ covers the ventricular surface of the posterior commissure (Figure 13). Well developed in submammalians and in most of mammals, it is also present in 3-5-month-old human fetus [114-116].

The organ is formed by a stratified columnar epithelium, hypendymal glial cells and capillaries, further contains some neurons and several nerve fibers. Afferent fibers are coming from the posterior commissure, pineal tract, habenular commissure and raphe nuclei, the latters exert an inhibitory effect on the organ. In addition GABA, dopamine, noradrenaline, LH-RH, vasopressin, vasotocin, oxytocin, mesotocin, substance P, α-neoendorphin and galanin were demonstrated in fibers of the subcommissural area. Neurotransmitters and neuropeptides present in the CSF were supposed to influence the activity of the SCO [117-120].

The cytoplasm of the ependymal cells is rich in rough-surfaced endoplasmic reticulum and produces a glico-lipoprotein complex. The secretory activity shows a seasonal variation in the cold-blooded reptiles and decreases in the lethargic state of the
animals [121]. The material is secreted into the ventricle and forms a thin and long fiber (Reissner's fiber) extending in the lumen of the mesencephalic aqueduct, fourth ventricle and central canal. The fiber is sticky and cells or cell debris in the CSF may be attached to it. It also binds and transports away monoamines present in the CSF [122]. There is a secretory activity in the cytoplasm of the hypendymal glial cells as well. Calcitonin generated-related peptide produced in the glial and ependymal cells may represent an endocrine-like product of the organ [123].

In several vertebrates the central canal is dilated at the distal end of the terminal filum (terminal ventricle, ampulla caudalis). In this enlargement the Reissner's fiber is coiled up forming a mass, the massa caudalis (FIGURE 14) and escapes through openings between ependymal cells [106,124,125]. Several data confirm the role of the organ in the pathogenesis of hydrocephalus [126-130]. The function of the fiber seems to be connected with the supposed mechanoreceptor function of the spinal CSF-contacting neurons (see in the corresponding chapter).

The recessus mesocoelicus at the caudal end of the subcommissural organ is a deepening covered by an ependymal layer similar to that of the subcommissural organ [131]. In some species there is another similar area more caudally: the recessus colliculi posteriores. The mesencephalic middle ridge formation is an additional circumventricular organ-like area situated on the ventricular surface of the optic tectum in cartilaginous fishes. As part of the mesencephalic trigeminal complex, it contains several large CSF-contacting neurons and supraependymal perikarya as well as nerve fibers. 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 [132]. The rostralmost end of the floor plate of the metencephalon contains special ependymal cells secreting a glycoprotein similar to that of the subcommissural organ [133].
B. AREA POSTREMA

Present in most of vertebrate classes and composed by two symmetrical parts, the area postrema is situated in mammals between area cinera and rhombencephalic tenia at the caudal end of the fourth ventricle (FIGURE 15). Ontogenetically appears very early during the 10th gestational week in human and in adults it can be visualized with contrast-enhanced MR [134-137]. The organ contains numerous fenestrated sinusoid capillaries characterized by a broad perivascular space. The glial limiting membrane in front of the perivasal space is crossed by nerve fibers, some of them are dendrites of neurons. Sitting in a network of glial cells, the neurons are of various types. Some of them are gamma-aminobutyric acid-, noradrenalin-, encephalin- and angiotensin II-containing neurons reciprocally connected by axodendritic synapses [138-140]. Tyrosine hydroxilase-immunoreactive perikarya were found to send processes to the perivasal space as well as to the ventricular surface [4,141]. Supraependymal clusters of CSF-contacting neurons interconnected by fascicles of nerve fibres were found in the rhesus monkey [142]. Similar cells and fibers are present at the top of the lateral recess of the fourth ventricle in the rabbit [76].

The area postrema has fiber connections with several nuclei (nucleus tractus solitarius, nucleus ambiguus, parabrachial nucleus, the cardiovascular center of the rostral ventrolateral medulla, locus coeruleus, mesencephalic nucleus of trigeminus, the griseum centrale, inferior and superior colliculi and dorsomedial hypothalamic nucleus [143-145]. Experimental results showed the participation of the organ in rather multiform autonomic and endocrine functions such as the regulation of cerebrospinal fluid production, blood pressure, heart rate, respiratory responses, body temperature, pancreatic exocrine activity, osmoregulation, renal sympathetic nerve activity, anxiety related behavior, sexual activity, etc. [7,31,146,147]. Morphologically, based on the lack of blood-brain barrier in the organ, a receptor function related to the chemical environment of the systemic circulation was supposed for the area postrema, but neurocytologically, the perivascular receptory dendrites of neurons present in the organ must also be taken into consideration for a specific sensory function.

Three types of chemosensitive nerve cells were identified in the organ: glucose responsive neurons that may participate in control of blood glucose and satiation, sodium (osmotic pressure)-responsive neurons that may contribute to control of sodium and water balance of the body fluid and may be involved in salt appetite, further, nausea-related neurons responding to excess distension of stomach and playing a role in formation of conditioned taste aversion [148]. Vagal cells innervating the fundus and corpus of the stomach in the rat are concentrated under the area postrema. A vagal input to neurons in the organ is monosynaptically relayed in the cat to parabrachial nucleus analogous to the pontine taste area in human, an intermediate relay station for gustatory information ascending from the solitary nucleus to VPM of the dorsal thalamus [149]. Lesion of the area postrema interferes with food intake induced by cerebroventricular infusion of 5-thioglucose [150,151]. Activation of the organ was also supposed to lead to nausea and vomiting through its projection to the neighboring nucleus of the solitary tract [152]. CSF-contacting neurons of the dorsal motor nucleus of the vagus nerve could receive chemical signals directly from the blood and CSF and influence gastrointestinal, cardiovascular and endocrine functions [153].

Area postrema also modulates cardiovascular functions by excitatory fibers to nucleus tractus solitarius, which has primary cardiovascular sensory input via the solitary tract [154]. During angiotensin II-induced elevation of arterial pressure, there is an attenuation of the baroreflex control of heart rate which results from resetting of the cardiac baroreflex mediated via the area postrema [155]. Adrenomedullin circulating in the blood and acting in cardiovascular regulations increases blood pressure when injected into the area postrema [156]. Subfornical organ neurons also respond to circulating pyrogens and through their efferent projections activate central pathways involved in fever [53]. It seems noteworthy that stimulation of area postrema decreases blood flow to choroid plexus and thus may play a role in regulation of volume in the central nervous system by modulating production of cerebrospinal fluid [157].
Special structures of the ventricular wall were described near the area postrema as area juxta-postrema and area subpostrema [158].

C. THE MEDULLO-SPINAL CSF-CONTACTING NEURONS

Present in the oblongate medulla, spinal cord and terminal filum, small intra- and subependymal neurons send their dendrites into the caudal end of the fourth ventricle and central canal (FIGURE 16). The luminal receptor pole of the CSF-contacting dendrite is supplied with 40-60 stereocilia being similar to those of known mechanoreceptors like the sensory cells of the lateral line organ of fish and amphibians, or the hair cells of the inner ear. The stereocilia contain parallle running fibrils and extend radially into the CSF. Similarly to lateral line cells, they immunoreact with acetilated tubulin and phalloidin. 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 such as AChE, monoamines, urotensin II and somatostatin. In the rat and mouse GABA, L-amino acid decarboxylase and methionine-enkephalin-Arg6-Gly7-Leu8 immunoactivity was detected in these neurons. There are VIP-immunoreacting CSF-contacting neurons in the monkey spinal cord [159-164].

The kino- and stereocilia of the neurons were often seen in contact with Reissner's fiber, the secretory material of the subcommissural organ. Running in the lumen of the central canal, the Reissner's fiber may act on the stereocilia of spinal CSF-contacting neurons like the tectorial membrane acts on hair cells, a relation suggesting a mechanoreceptor task (flow or pressure of the CSF?) of the spinal CSF-contacting neurons. The axons of the neurons run to the outer surface of the spinal of cord to form terminals of neurohormonal type. Collaterals of these axons are going to
intraspinal neurons. 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. 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. The outflow of the Reissner's fiber keeps open this terminal hole of the filum permitting the outflow of the CSF [16,80,106,159].

The human subcommissural organ is only active in embryonic life and in the newborn [90]. Takeuchi and Takeuchi [126] found dysplasia of the subcommissural organ in induced hydrocephalus of rats. A decreased CSF flow was found through the central canal deprived of Reissner's fiber [165]. The question arises as to whether a subcommissural organ that becomes inactive at too early stage may cause a congenital hydrocephalus (see also in the chapter of the subcommissural organ).

D. UROPHYSIS

The urophysis, or neurophysis caudalis of fish - a ventral thickening of the caudal spinal cord - contains large neurosecretory perikarya (Dahlgren-cells) and a zone of neurosecretory terminals similar to the neurohypophysis (FIGURE 17). The neurosecretory perikarya near the central canal send CSF-contacting dendritic terminals into the lumen. These dendrites are similar to those of hypothalamic neurosecretory cells and different from the spinal CSF-contacting dendrites bearing several stereocilia. Some chemical stimuli may be perceived from the inner spinal CSF by the dendrites of the Dahlgren-cells influencing the neurohormonal output of the urophyseal axons [16,166,167].

In the Dahlgren cells the vasodilator and ACTH-releasing neuropeptide urotensin I, the somatostatin-like dodecapeptide urotensin II, a sauvagine-like material, and, further, corticotropin releasing factor receptors were found [168-172]. In the core of the granules of the neurosecretory axons neuronal nitric oxide synthase, and urotensins I, II were localised [173]. Some of the neuronal perikarya contain methionine-encephalin [174]. Axons of serotoninergic neurons present among Dahlgren cells also contribute to the neurohormonal terminals of the urophysis [175].

Osmotic stress resulted in increased Urotensin I and II immunoreaction and ultrastructural changes in the caudal neurosecretory system of the seawater fish maintained in freshwater environment [171,176]. An acidified (pH 5.5) environment stimulates the synthetic activity and release of urotensin II from the urophysis [177]. Dahlgren cells contain calcium-sensitive receptor protein supposed to be responsive to calcium in the central nervous system. Dahlgren cells also produce parathyroid hormone-related protein which may be released from axons abutting at pericapillary spaces in the urophysis [178].

4. GENERAL CONCLUSIONS

The comparative neurohistology of the circumventricular organs of various vertebrates and human presented in this review show the close contact of their cells with the internal and/or external CSF space. Some of them, like the vascular organ of the terminal lamina, vascular sac, pineal organs and spinal CSF-contacting neuronal areas as well as the urophysis form neurohormonal release sites being similar to those of median eminence and neurohypophysis. In these areas effector axon terminals of secretory neurons pierce the perivascular glial limiting membrane and are attached by half-desmosomes to the basal lamina of the vascular surface of the nervous tissue. Neurohormones are secreted from these nerve terminals by exocytosis of secretory granular vesicles into the perivasal space and enter from here by diffusion into vessels. The perivascular spaces are the continuation of the subarachnoidal space, therefore, the external CSF may have a modulatory effect on the process of neurohormonal release [16,78,179].

The lack of blood-brain barrier in these areas primarily seems to serve the hormon release to the blood circulation. In addition to the neurohormonal terminals of circumventricular organs there are many more neuronal areas with access to the blood circulation without blood-brain barrier [180]. On the basis of experimental works, the hormone releasing effector areas of the circumventricular organs were generally taken as receptor zones for bioactive substances circulating in the blood. However,
considering the basic receptor/effector polarization of the cytology of neurons, the subfornical organ and area postrema sending receptor dendrites to the perivascular surface may correspond to the morphological basis for perceiving the composition of the perivasal fluid. Neurons of the subfornical organ also send receptor dendrites to the ventricular CSF. We think that, by these terminals and together with the perivasal dendrites, the comparative perception of the composition of both fluids seems to be possible.

All neurons of the paraventricular organ form dendritic terminals bearing a 9+0-type sensory cilium in the third ventricle. Similar neurons are also present in the lateral septal- and preoptic recess organ, infundibular and mamillary recesses and further, around the central canal and in the urophysis. Those of the lateral septum, pre- and supraoptic nuclei of submammalians contain opsins and were found to represent the deep brain photoreceptors, detecting the illumination of the brain and CSF and influencing photoperiodic regulation of brain and body functions [10]. Those of the paraventricular organ, infundibular and mamillary recesses are supposed to be chemoreceptors for the internal CSF. The medullospinal CSF-contracting neurons situated around the central canal show cytological similarity to known mechanoreceptors like the lateral line organ of fishes and amphibians or the sensory cells of the inner ear. They are supposed to perceive the flow or pressure of the CSF [79,109].

Periventricular neurons sending a sensory cilium into the intercellular space of the nervous tissue may percept the chemical composition of the intercellular fluid important in the metabolism and in non-synaptic signal transmission of the brain. As gap-junctions are lacking in the ventricular ependyma, the subependymal intercellular fluid communicates with ventricular CSF. It may also be supposed that some subependymal cells of a neuron group having intraventricular dendrites modulate their activity according to the composition of the ventricular CSF, while others, being more distally depend on the intercellular fluid. The connection found between both neuron types may serve the detection of differences between the two fluids [78,79].

The subcommisural organ contains ependymal cells secreting the Reissner's fiber which extends into the mesencephalic aqueduct, fourth ventricle and central canal. In lower vertebrates, there is an opening at the caudal end of the terminal filum, where the Reissner's fiber is flowing out, and keeps open this hole for the outflow of the CSF. The fiber may facilitate the supposed mechanoreceptive task of the spinal CSF-contacting neurons and seems to be involved in the pathogenesis of hydrocephalus [56, 105].

From the point of view of comparative neurohistology it seems to be important that there are more circumventricular organs in lower vertebrates than in human. In the simple central nervous system of the chordate lancelet (Branchiostoma lanceolatum) nearly all neurons of the tube-like brain are arranged around the lumen and their function depends on the composition of the primary cerebrospinal fluid reflecting the activity and metabolism of the whole brain tissue. The neurons of more differentiated vertebrates migrated away from the ventricle forming various brain nuclei and cortical areas already depending on the newly formed vascular supply. Remaining in close contact with the ventricular system the circumventricular organs may represent an archaic regulatory system to assure the homeostasis of the CSF and by this the neighbouring intercellular fluid being important for the metabolism and nonsynaptic signal transduction of the brain tissue [79].

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6. REFERENCES


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