

## Review

# The circumventricular organs

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**Summary.** The circumventricular organs (CVOs) are midline structures located around the third and fourth ventricles that are characterized by a lack of blood-brain barrier. The pineal gland, median eminence, neurohypophysis and the subcommisural organ are classified as secretory, whereas the subfornical organ, area postrema and the organum vasculosum of the lamina terminalis as the sensory CVOs. Glial cells consisting of astrocytes and microglia/macrophages are present in all these organs. The pineal gland, neurohypophysis and the median eminence lack the presence of neurons that are present in the rest of the CVOs. Most of the CVOs are lined by ependymal cells except for the pineal and the neurohypophysis. Modified ependymal cells known as tanycytes are present in the ependymal lining. These organs are important sites for communication with the cerebrospinal fluid as well as between the brain and peripheral organs via blood-borne products as they lack the blood-brain barrier.

**Key words:** Pineal gland, Median eminence, Neurohypophysis, Subcommisural organ subfornical organ, Area postrema, Organum vasculosum of the lamina terminalis

## Introduction

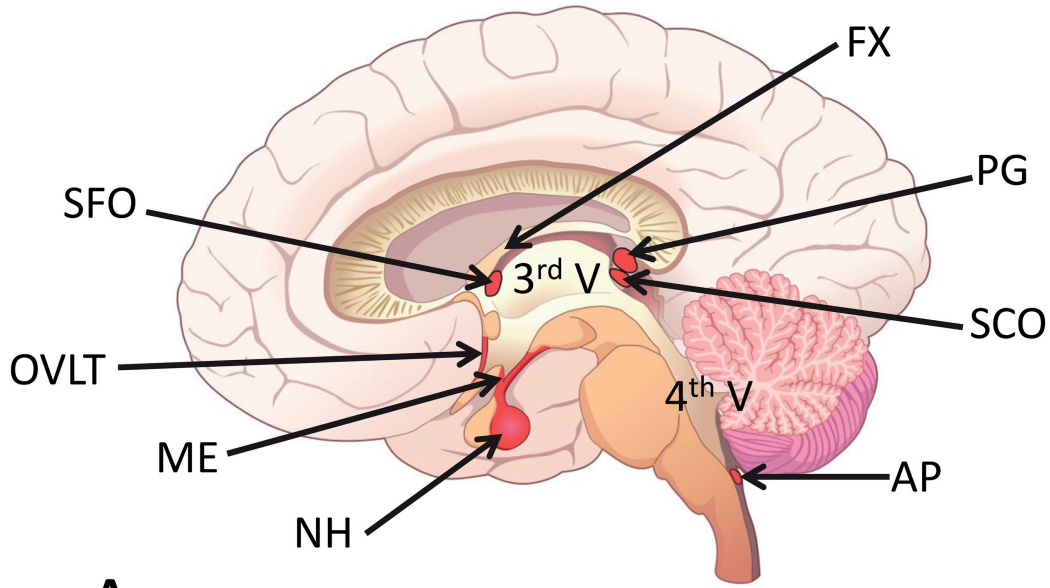
The circumventricular organs (CVOs) are areas of the brain associated with the third and the fourth ventricles. They are located in the midline and are characterized by absence of the blood-brain barrier as the endothelium of the capillaries is fenestrated (Duvernoy and Risold, 2007; Ciofi et al., 2009; Ciofi, 2011) and lacks the tight junction complexes (Langlet et al., 2013). The CVOs are separated from the brain tissue by modified ependymal cells called the tanycytes and are considered to play an important role in maintaining the homeostasis of the body through blood-brain communication (Gross and Weindl, 1987). Depending on their function, the CVOs are classified as sensory and secretory by several authors (Cotrell and Ferguson, 2004). The subfornical organ, area postrema and the organum vasculosum of the lamina terminalis (Fig. 1A) are the sensory CVOs that can pass information to other brain regions and the autonomic nervous system through sensing plasma molecules. The pineal gland, median eminence, neurohypophysis and the subcommisural organ (Fig. 1A) fall under the secretory category as they secrete hormones and glycoproteins into the blood. In addition to these, some authors consider the choroid plexus as a circumventricular organ as it has fenestrated capillaries.

## Secretory circumventricular organs

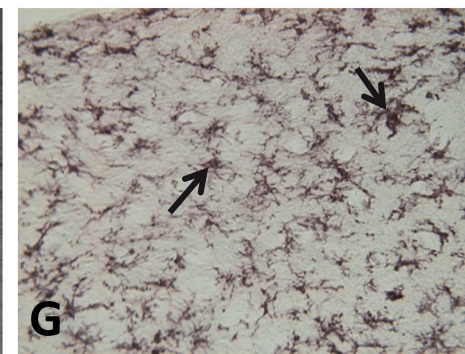
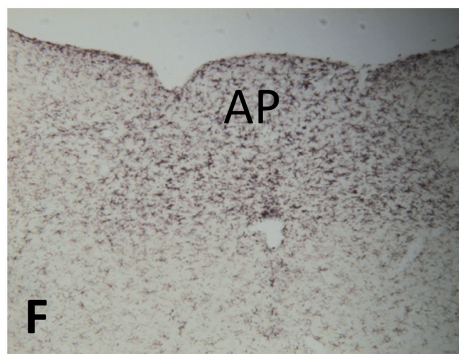
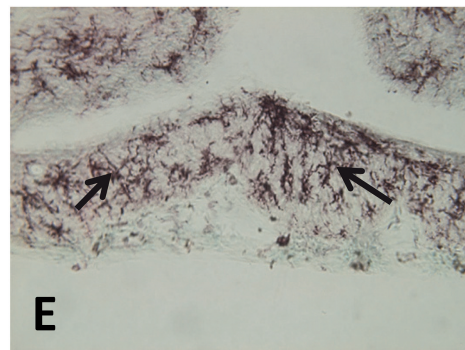
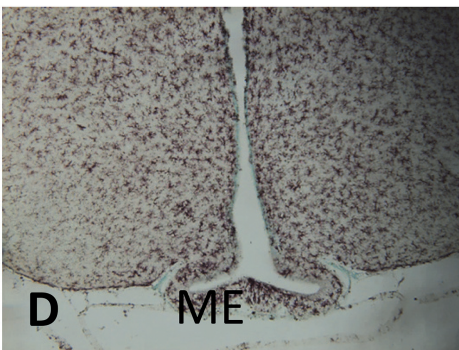
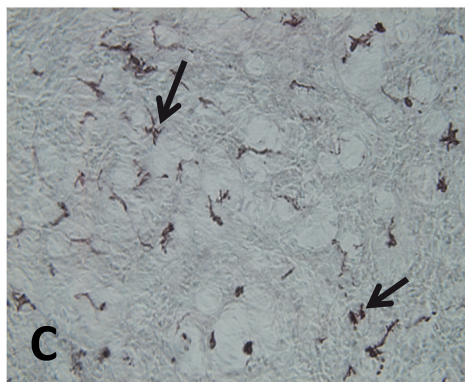
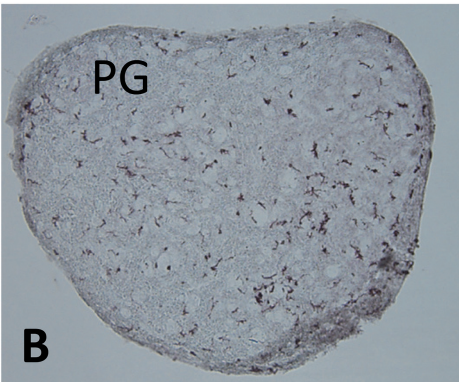
### *Pineal gland*

The pineal gland is located close to the posterior aspect of the third ventricle (Fig. 1A) and functions as a synchronizer of the chronobiology of organisms through

Circumventricular organs



**A**



**Fig. 1. A** A diagrammatic representation of a sagittal section of the brain showing the location of various circumventricular organs in association with the third ventricle (3rd V) and fourth ventricle (4th V). AP, area postrema; AQ, aqueduct; FX, fornix; ME, median eminence; NH, neurohypophysis; PG, pineal gland; OVLT, organum vasculosum of the lamina terminalis; SCO, subcommissural organ; SFO, subfornical organ. **B-G** show OX 42 microglia/macrophages in the pineal gland (**B and C**), median eminence (**D and E**) and the area postrema (**F and G**). Microglia/macrophages (arrows) can be seen at higher magnification in **C, E and G**. **B, D, F, x 100; C, E, G, x 400.**

synthesis of melatonin. The cell types identified in the pineal gland are the pinealocytes and interstitial cells further classified as the astrocytes and microglia/macrophages (Pedersen et al., 1993; Kaur et al., 1997). Melatonin which is synthesized by the pinealocytes, has several actions such as modulation of mood, sleep, sexual behaviour, reproductive alterations and circadian rhythms. It also acts as an anti-oxidant and regulates immune functions. The secretion of melatonin is dependent on sympathetic innervation of the pineal gland from the superior cervical ganglion, the nerve fibres making synaptic contacts with the pinealocytes (Ling et al., 1989, 1990). Melatonin secretion is also regulated by light and darkness that decrease or increase the melatonin secretion, respectively.

Pinealocytes are the chief cells of the pineal gland that have been reported to be of two types -light and dark pinealocytes (Al-Hussain, 2006). Both types of cells synthesize and secrete melatonin, have abundant cytoplasm containing a well-developed Golgi complex, mitochondria, dense-cored vesicles, multivesicular bodies, rough endoplasmic reticulum and a variable number of lipid droplets (Ling et al., 1989). Alteration in cytoplasmic organelles such as increased number of mitochondria, lipid droplets and rough endoplasmic reticulum has been reported to occur at night or under experimental light restriction suggesting enhanced pinealocyte activity (Krakowski and Cieciora, 1985; Swietoslowski and Karasek, 1993; Kus et al., 2004).

Melatonin synthesized by the pinealocytes has antioxidant (Gilad et al., 1997; Reiter et al., 1999, 2003), anti-inflammatory (Cuzzocrea et al., 1998) and anticonvulsant actions (Yildirim and Marangoz, 2006) and has been used in the treatment of sleep disorders in children and adults (Jan et al., 1994; Cardinali et al., 2006). It is also documented to prevent mitochondrial impairment in oxidatively damaged mitochondria (Acuna-Castroviejo et al., 2007) and is beneficial in several types of cancers such as ovarian carcinoma (Petranka et al., 1999), endometrial carcinoma (Kanishi et al., 2000), prostate cancer (Siu et al., 2002), intestinal tumors (Anisimov et al., 1997), breast cancer (Kiefer et al., 2002) and lung cancer (Lissoni et al., 2003). People suffering from circadian rhythm-related disorders such as jet lag and those involved in shift work (Croughs and De Bruin, 1996; Arendt et al., 1997) have been reported to benefit from the use of melatonin. Other than all these, experimental studies have shown that melatonin has the potential to reduce cataract formation (Abe et al., 1994) and delay photoreceptor loss in experimentally induced retinitis pigmentosa (Liang et al., 2001). Neuroprotective actions of melatonin have been well demonstrated in conditions such as amyotrophic lateral sclerosis (Weishaupt et al., 2006) Parkinson's disease (Mayo et al., 2005), Alzheimer's disease (Feng et al., 2004), ischemic brain injury (Pei and Cheung, 2004), neuropsychiatric disorders and head injury (Beni et al., 2004). These may be due to amelioration of several factors such as oxidative stress, pro-inflammatory

cytokine production, free radical generation and nitric oxide production (Kaur et al., 2010, 2013). In addition, melatonin has been shown to reduce cerebral edema by reducing blood-brain barrier permeability in hypoxic conditions (Kaur et al., 2006) thus protecting neurons from the toxic effects of serum derived substances.

Other than the pinealocytes, macrophages/microglia expressing complement type 3 (CR3) receptors and major histocompatibility complex (MHC) class I and II antigens are also found in the parenchyma and the perivascular spaces in the pineal gland (Fig. 1B,C) (Sato et al., 1996; Kaur et al., 1997; Kaur and Ling, 1999; Moller et al., 2006) suggesting that these cells have phagocytic and immunoregulatory functions (Pedersen et al., 1993; Moller et al., 2006). Through secretion of cytokines, the macrophages/microglia may modulate the structure and function of the pinealocytes (Tsai et al., 2001a,b). *In vivo* and *in vitro* studies have shown that the pineal microglia express cytokines such as tumor necrosis factor- $\alpha$  (TNF)- $\alpha$  and interleukin-1 $\beta$  (IL-1 $\beta$ ) (Tsai and McNulty, 1999; da Silveira Cruz-Machado et al., 2012). TNF- $\alpha$  has been suggested to modulate melatonin synthesis through activation of TNF receptors of the subtype 1 (Carvalho-Sousa et al., 2011; da Silveira Cruz-Machado et al., 2012) and toll-like receptor 4 (TLR4) on the pinealocytes (da Silveira Cruz-Machado et al., 2010). Another cytokine interferon- $\gamma$  that activates macrophages/microglia (Xu and Ling, 1994) has been reported to enhance melatonin production (Withyachumnarnkul et al., 1990a,b).

Astrocytes have been reported to form a barrier between the pineal parenchyma and the perivascular spaces (Papasozomenos, 1983; Zang et al., 1985; Lopez-Munoz et al., 1992). It has been suggested that besides macrophages/microglia, astrocytes in the pineal may also take part in the immune surveillance system (Jiang-Shieh et al., 2005) that is supported by expression of IL-1 $\beta$  on them (Tsai and McNulty, 1999). Astrocytes and pinealocytes were also shown to express  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), N-methyl-D-aspartate (NMDA), and group I metabotropic glutamate receptors in the pineal gland (Kaur et al., 2005; Villela et al., 2013). It has been reported that high levels of glutamate are present in the pineal cells of mammalian pineal gland (Schell et al., 1997; Yatsushiro et al., 1997) and that glutamate can modulate melatonin synthesis and interactions between pinealocytes and astrocytes through activation of astrocytic NF- $\kappa$ B and subsequent release of TNF- $\alpha$  (Villela et al., 2013).

#### *Median eminence*

The median eminence is involved in the regulation of several processes such as reproduction, lactation, growth and stress and is a pivotal interface between the neural and endocrine systems (Yin and Gore, 2010). It is one of the secretory CVOs located between optic chiasma and mammillary bodies at the base of the hypothalamus above the pituitary stalk (Fig. 1A). The

neurohypophysis is continuous with it through the infundibular stalk while the pars distalis is connected to it via the hypophyseal portal system. Neurosecretory nerve endings of neurons in the arcuate, paraventricular and supraoptic nuclei and pre-optic area of the hypothalamus either end in the median eminence on the capillary plexus or pass through it to reach the pars nervosa. The parvocellular neurons in the paraventricular nucleus secrete releasing/inhibitory (regulatory) hormones that are brought to the median eminence through axon terminals before being sent to the primary capillary plexus and conveyed to secondary capillary plexus in the pars distalis by portal veins. In addition, dopamine secreted by neurons in the arcuate nucleus of the hypothalamus is also transported to the pars distalis through the hypophyseal portal veins.

The median eminence consists of a large number of unmyelinated axons of the neurosecretory cells in the supraoptic and paraventricular nuclei that reach the pars nervosa by passing through it. Axons of neurons containing the regulatory hormones in secretory vesicles have been reported to terminate in the perivascular spaces or contact the basement membrane of fenestrated capillaries of the primary capillary plexus. These capillaries are surrounded by irregular perivascular spaces that contain collagen fibres, a few fibroblasts and mast cells. Microglia, astrocytes and cells lining the third ventricle i.e. ependymal cells and tanycytes ((also known as astrocytic tanycytes (Zaborszky and Schiebler, 1978)) are present in the median eminence (Bitsch and Schiebler, 1979). Microglial cells were reported to be present in the parenchyma as well around the blood vessels and were strongly labelled by OX-42 (Fig. 1 D,E) and F4/80 that are specific microglia markers (Mander and Morris, 1995). It was suggested that the microglia in close association with the blood vessels, called the perivascular microglia, were capable of antigen presentation to T lymphocytes (Mander and Morris, 1995).

Tanycytes line the lateral walls and the floor of the third ventricle between the rostral and caudal limits of the median eminence (Fekete and Lechan, 2014). They have a small cell body containing numerous microtubules, some lipid droplets and granules (Kozłowski et al., 1976) and their end feet contact the basal lamina of the fenestrated capillaries of the primary capillary plexus. They express intense vimentin immunoreactivity and are weakly immunoreactive to glial fibrillary acidic protein (GFAP) whereas the astrocytes have been reported to be GFAP positive but vimentin-negative and their processes were closely associated with the neurohypophysial axons (Chauvet et al, 1995). Several hypothalamic functions such as regulating neurosecretion, mediating seasonal cycles of reproduction and metabolic processes are modulated by tanycytes (Langlet, 2014; Bolborea et al., 2015; Goodman and Hajihosseini, 2015). They express estrogen receptors and may be involved in the release of gonadotropin-releasing hormone (GnRH) to the portal veins (Rodríguez et al.,

2005). Expression of thyroxine deiodinase type II, an enzyme involved in generation of triiodothyronine (T3) from thyroxine, has been reported on the tanycytes indicating that they are the key cells in regulation of brain T3 (Rodríguez et al., 2005). Their involvement in sensing cerebrospinal fluid (CSF) glucose concentrations has also been reported as they express glucose transporter-2 and ATP-sensitive K(+) channels (Rodríguez et al., 2005). Tanycytes have also been thought to represent a population of hypothalamic stem cells for neurogenesis (Rizzoti and Lovell-Badge, 2017). Tanycytes of the median eminence have also been reported to express tight junction proteins such as occludin, zonula occludens-1 (ZO-1), and claudin 1 and 5, suggesting that they form a barrier between the portal capillaries and the brain (Mullier et al., 2010). Tanycytes have also been suggested to be involved in glutamate signalling as they express AMPA GluR2/3 and kainate receptor subunits GluR6/7 (Eyigor and Jennes, 1988; Kawakami, 2000).

Astrocytes in the median eminence have been considered as key regulators of GnRH and luteinizing hormone-releasing hormone (LHRH) secretion through production of growth factors, such as transforming growth factor (TGF)- $\beta$  and activation of TGF- $\alpha$ -erbB-1 signalling that may require prostaglandin release from astrocytes (Beauvillain and Prévot, 2004; Prévot et al., 2007). Astrocytes may also have a significant role in regulation of food intake through expression of leptin receptors and neuropeptide Y Y1 receptor (Cheunsuang and Morris, 2005). It has been suggested that these cells may be involved in processes such as hormone release through expression of brain-derived neurotrophic factor (BDNF) (Givalois et al., 2004) although the mechanism underlying such a release has not been elucidated.

#### *Subcommisural organ*

The subcommisural organ (SCO), an ependymal structure covering the posterior commissure, is a secretory structure located in dorsocaudal region of the third ventricle close to the entrance of aqueduct (Fig. 1A) (Rodríguez et al., 1998). It is located at the interface between the CSF and the blood and is composed of two layers of cells known as ependyma and hypendyma. The hypendyma is the layer beneath the ependyma and is composed of numerous capillaries and glial cells.

The specialized ependymal cells are bipolar secretory cells that release their secretions into the CSF through their apical poles and contact the local capillaries through their basal processes (Leonhardt, 1980; Rodríguez et al., 1992, 2001; Guerra et al., 2015) whereas the hypendymal cells contact the blood vessels and the subarachnoid space through their processes (Rodríguez et al., 1992). The ependymal cells are linked to each other through tight junctions and they possess abundant dilated cisternae of rough endoplasmic reticulum, a Golgi complex, mitochondria and secretory granules (Rodríguez et al., 1998). The secretory material

of the ependymal cells is released into the ventricle and consists of two types of proteins: soluble and insoluble. The soluble proteins circulate in the CSF whereas the insoluble glycoproteins condense to form a thread like structure called the Reissner's fiber (Sterba, 1969) that extends along the aqueduct, fourth ventricle, and the whole length of the central canal of the spinal cord (Sterba, 1969; Leonhardt, 1980; Caprile et al., 2003; Guerra et al., 2015) and is finally degraded at its terminal part near the filum terminale (Molina et al., 2001; Caprile et al., 2003).

Subcommissural-spondin (SCO-spondin), transthyretin (TTR) and basic fibroblast growth factor (bFGF) are some of the proteins secreted by the ependymal cells into the CSF (Guerra et al., 2015). SCO-spondin, a glycoprotein, forms the Reissner's fiber and has been reported to contribute to commissural axon growth and neural development (Gobron et al., 1996; Vera et al., 2013). It has been considered as a crucial factor in the embryonic CSF which helps to regulate the balance between proliferation and differentiation of the brain neuroepithelial cells (Vera et al., 2013). CSF production, composition and circulation have also been proposed to be regulated by Reissner's fiber (Cifuentes et al., 1994; Rodriguez and Yulis, 2001; Caprile et al., 2003) but detailed investigations on this are lacking. The contribution of SCO-spondin to the posterior commissure development has been suggested (Meiniel et al., 2008; Caprile et al., 2009; Hoyo-Becerra et al., 2010; Stanic et al., 2010; Grondona et al., 2012) based on *in vitro* and *in vivo* studies in animals reporting that loss of SCO-spondin causes a marked decrease in the number of axons or axonal defasciculation (Vera et al., 2013).

The ependymal cells of the SCO synthesize the protein TTR (Montecinos et al., 2005) that is involved in the transport of thyroid hormone and retinol in the CSF (Chanoine and Braverman, 1992; Bernal, 2002). In addition animal studies have shown bFGF-like immunoreactivity in SCO ependymal cells and loss of bFGF-immunopositive ependymal cells has been suggested to be an underlying factor in the development of hypertension (Cuevas et al., 1996). Abnormal development of SCO results in its failure to form Reissner fiber that is considered as an underlying factor in the development of congenital hydrocephalus (Wagner et al., 2003; Meiniel, 2007). Immunoneutralization of the SCO- Reissner fiber complex in the fetal period by sustained delivery of anti-Reissner fiber antibodies into the CSF has been reported to result in absence of Reissner fiber, stenosis of the aqueduct and hydrocephalus (Pérez-Figares et al., 2001).

Expression of angiotensin II (ANG II) receptors (Ghiani et al., 1988; Castañeyra-Martín et al., 2005), endothelin 1 and bradykinin (Schöniger et al., 2009) on the SCO ependymal cells has been suggested to influence their secretory activity that appears to be under neural control through serotonergic, GABAergic and catecholaminergic innervation (Møllgård and Wiklund 1979; Balaban et al., 1994; Jiménez et al., 2001; Tomé et

al., 2004).

Like the ependymal cells, the hypendymal cells have also been reported to be polarised, having an apical pole and basal processes that end on the blood vessels or the subarachnoid space. The nature of their secretions has been reported to be similar to that of the ependymal cells but they are released into the subarachnoid CSF and not into the ventricle (Rodríguez et al., 1998). The capillaries in the SCO are surrounded by a perivascular space but unlike other CVOs their endothelium is not fenestrated, suggesting that a blood-brain barrier is present here (Rodríguez et al., 1998).

### Neurohypophysis

Neurohypophysis or the pars nervosa (Fig.1A) is connected to median eminence of the hypothalamus through the pituitary stalk. It consists of axons of magnocellular neurons in the supraoptic and paraventricular nuclei of the hypothalamus and is the site where the hormones vasopressin and oxytocin are stored in dense cored vesicles in axon swellings known as Herring bodies (Hatton, 1988). The hormones are released from axonal terminals contacting the basal lamina into the perivascular spaces surrounding the fenestrated capillaries and from there they enter bloodstream (Hatton, 1988). The perivascular spaces have been reported to contain pericytes, fibroblasts and mast cells (Seyama et al., 1980). The size and number of neurosecretory axon terminals in contact with the basal lamina have been reported to increase in conditions of water deprivation and during parturition (Tweedle and Hatton, 1982, 1987).

Other than the axons and capillaries, glia-like cells known as pituicytes are present in the neurohypophysis. Based on ultrastructural studies, it was suggested that the pituicytes may be involved in control of the neurohypophyseal secretion as these cells were found engulfing or surrounding neurosecretory axons under normal conditions and releasing them when increased hormone output was required (Hatton, 1988). The pituicytes were also reported to be in close contact with the perivascular space of capillaries (Wittkowski, 1998). During low hormone demand the pituicytes have been shown to interpose their processes between the axon terminals and the basement membrane whereas they retract their processes when the hormone demand is high, suggesting that they are involved in controlling hormone release (Hatton et al., 1984). Expression of specific membrane-bound receptors for opioids, vasopressin, and beta-adrenoceptors has been demonstrated on the pituicytes (Wittkowski, 1998). Earlier studies considered the pituicytes to be astrocytic in nature (Suess and Pliska, 1981; Salm et al., 1982) and this view has been supported by several studies that have demonstrated the expression of astrocyte specific markers GFAP and microtubule-associated protein-2 on these cells (Redecker, 1987; Matsunaga et al., 1999; Saland et al., 2000). In addition, microglia and

macrophages, have also been identified in the neurohypophysis (Mander and Morris, 1996) the majority of which have been reported to be located close to the capillaries (Pow et al., 1989; Moffett and Paden, 1994). These cells were shown to express CR3 receptors and MHC I and II antigens; the cells expressing MHC II antigens were located close to the blood vessels (Moffett and Paden, 1994; Mander and Morris, 1995). It was suggested that the perivascular microglia were capable of antigen presentation to T lymphocytes. The microglia were also found to engulf the neurosecretory axon terminals and contain some neurosecretory granules and it was suggested that they may be involved in remodelling of terminal arborizations of axons as well as in degrading hormones and peptides contained in them (Pow et al., 1989).

### Sensory circumventricular organs

#### *Area Postrema*

The area postrema is located at the caudal end of the fourth ventricle (Fig. 1A). In most mammals other than rodents and lagomorphs, it is represented by a pair of oval structures on either side of the obex protruding into the fourth ventricle. In rodents and lagomorphs, the area postrema is a single midline structure. The morphology of the area postrema in various species such as the rabbit (Shimizu and Ishii, 1964), rat (Dempsey, 1973), mouse (Rohrschneider et al., 1972) and monkey (Klara and Brizzee, 1975; Ling and Wong, 1987) has been reported to be similar. In humans it has been described only in cadaveric specimens (Longatti et al., 2015) or by neuroendoscopy (Longatti et al., 2008). The area postrema is covered with a specialised ependymal lining that separates it from the ventricle, is highly vascularised and is closely associated with the nucleus of the tractus solitarius (NTS) and dorsal motor nucleus of the vagus nerve. It plays an important role in modulating the autonomic functions by the central nervous system (Price et al., 2008). Its role in cardiovascular regulation (Ferguson, 1991), vomiting reflex (Borison and Brizzee, 1951), fluid balance (Curtis et al., 1999), feeding and metabolism (Johnstone et al., 2006; Smith et al., 2016) and immune responses (Goehler et al., 2006) is well documented.

The ependymal cells show microvilli and are joined by tight junctions at their apical portions (Klara and Brizzee, 1975; McKinley et al., 2003). Multivesicular structures appearing to be in direct continuity with the ependymal cells were reported to project into the ventricle (Klara and Brizzee, 1975). The capillaries in the area postrema are fenestrated and are surrounded by perivascular spaces that contain mast cells, macrophages, fibroblasts and collagen fibrils (Klara and Brizzee, 1975; Ling and Wong, 1987). Unlike capillaries in the brain parenchyma, the tight junctions between the endothelial cells lack the expression of tight junction proteins such as claudin-5, occludin, and ZO-1 (Langlet

et al., 2013).

Small neurons and glial cells are present in the area postrema (Brizzee and Klara, 1984; Ling and Wong, 1987). The neurons have been reported to send major efferents to NTS, the lateral parabrachial nucleus (LPBN) (Leslie and Osborne, 1984; Shapiro and Miselis, 1985) and the hypothalamus, whereas minor efferents to several other regions such as nucleus ambiguus, dorsal motor nucleus of the vagus, dorsal regions of the tegmental nucleus, cerebellar vermis and ventrolateral catecholaminergic column in the medulla are also documented (van der Kooy and Koda, 1983; Shapiro and Miselis, 1985). Afferent input to the area postrema has been documented to come from the NTS and LPBN, as well as parvocellular regions of the paraventricular nucleus and dorsomedial nucleus of the hypothalamus (van der Kooy and Koda, 1983; Shapiro and Miselis, 1985). Whereas the majority of the axons present in the area postrema have been reported to be unmyelinated (Dempsey, 1973), some myelinated axons in some species such as the rabbit and squirrel monkey may be present (Shimizu and Ishii, 1964; Klara and Brizzee, 1975). Other than the neurons, two types of glial cells are present in the area postrema: astrocytes and microglia/macrophages (Willis et al., 2007a; Al-Saleh et al., 2003). Occasional occurrence of oligodendrocytes in some species has been reported (Brizzee and Klara, 1984).

Different neuronal phenotypes expressing cholecystokinin, enkephalin, GABA, glutamate, glycine, and serotonin have been identified in the area postrema (Lanca and van der Kooy, 1985; Lind et al., 1985; Newton et al., 1985; Newton and Maley, 1985; Oldfield et al., 1989; Walberg and Ottersen, 1992). In addition to the above, peptide and hormone receptors such as ANG II adiponectin, adrenomedullin, endothelin, ghrelin and arginine vasopressin (AVP) have been reported (Price et al., 2008). Serotonergic neurons have been reported to function as sodium detectors and are implicated in the regulation of salt intake (Miller and Loewy, 2014). The area postrema is thought to be the central site modulating the baroreflex control of heart rate through the actions of ANG II and AVP (Cox et al., 1990; Fink et al., 1987; Matsukawa and Reid, 1990; Peuler et al., 1990). ANG II and AVP are vasoactive peptides that act on the area postrema to regulate blood pressure through modulating sympathetic and vagal activity (Bishop and Hay, 1993; Bishop and Sanderford, 2000; Hasser et al., 1997). In addition, peptides such as endothelin and adreno-medullin have been suggested to modulate blood pressure through activation of their respective receptors that are expressed on the area postrema neurons (Ferguson and Smith, 1990; Allen et al., 1997). The regulatory process of body fluid balance by the area postrema has been suggested to be linked to cardiovascular regulation as the peptides such as ANG II and AVP are involved in both processes (Price et al., 2008). The area postrema is able to detect emetic toxins in the blood as well as in the CSF and its activation leads

## *Circumventricular organs*

to nausea and vomiting through its projection to the NTS (Miller and Leslie, 1994). Activation of dopamine receptors in the area postrema has been suggested to mediate the emetic action of several drugs (Yoshikawa et al., 1996). Besides the above, it plays an important role in regulating feeding and metabolism as the neurons can sense peptide and nonpeptide signals through cholecystokinin, adiponectin and ghrelin among many others, and subsequently transmit them to the central nervous system (Price et al., 2008).

GFAP-positive astrocytes are present in the area postrema (Willis et al., 2007a,b) and have been reported to make a limited contact with the fenestrated capillaries (Willis et al., 2007b) unlike the capillaries in the brain where most of their surface is covered by the astrocyte end feet. The microglia/macrophages in the area postrema (Fig. 1F,G) are located either in the parenchyma or in the perivascular spaces and are known to express CR3 receptors, ED1 antigen and MHC I and II antigens (Pedersen et al., 1997; Al-Saleh et al., 2003). Both astrocytes and microglia in the area postrema express TLR4 (Nakano et al., 2015) which triggers signalling pathways leading to activation of proinflammatory cytokines (Rivest, 2003). The perivascular and parenchymal microglia/macrophages in the area postrema of lipopolysaccharide-treated rats have shown the expression of IL-1 $\beta$  suggesting that the area postrema is an immune sensory structure (Goehler et al., 2006).

### *Subfornical organ*

The subfornical organ is a round or oval midline structure adherent to the ventral surface of the fornix and bulging into the lumen of the third ventricle at the level of the interventricular foramen (Fig. 1A). Its structural organization has been reported to be similar in most species (Casali et al., 1989). It is an important sensor of blood-borne angiotensin and the principal site that monitors the sodium levels in the plasma and CSF and controls water and salt intake (Hiyama et al., 2004; Hiyama and Noda, 2016).

The subfornical organ is composed of neurons, glia, neuropil and ependymal cells that cover its ventricular surface. The neuropil is formed by dendrites, axons and glial cell processes (Dellmann, 1998). Fenestrated capillaries surrounded by perivascular spaces are present. The ependymal cells appear squamous or low cuboidal with microvilli in the central region of the organ whereas ciliated cuboidal ependymal cells are present towards the lateral sides (Dellmann and Simpson, 1976) and some tanocytes are also present (Dellmann, 1998). It has been reported that supraependymal neurons are present and the choroid plexus attaches to the subfornical organ through highly vascularized connective tissue (Dellmann and Simpson, 1976).

The neurons in the subfornical organ send efferents to the median preoptic nucleus that reach the organum

vasculosum of the lamina terminalis (OVLT), the suprachiasmatic and supraoptic nuclei (Lind and Johnson, 1982), the nucleus of the stria terminalis (Swanson and Lind, 1986) and the paraventricular nucleus of the hypothalamus (McKinley et al., 2012). The neurons have been reported to express choline acetyltransferase (Weindl et al., 1992), nitric oxide synthase (Jurzak et al., 1994), and acetylcholinesterase (Achaval and Schneider, 1984). Although very few angiotensin II-immunoreactive neurons located in the peripheral areas of the subfornical organ have been demonstrated (Lind et al., 1984), a high expression of type I angiotensin II receptors (AT1) has been described (van Houten et al., 1980; Mendelssohn et al., 1984; Plunkett et al., 1987). Acute dehydration upregulates these receptors (Hwang et al., 1986; Nazarali et al., 1987) and sodium deprivation ameliorates their expression (Ray et al., 1990). It is well documented that ANG II stimulates Na and water intake (Hiyama et al., 2004). Besides the above, expression of calbindin and calretinin in the neurons has been reported (McKinley et al., 2003) and these may have a potential role in the maintenance of ionic homeostasis.

Astrocytes, microglia/macrophages and a few oligodendrocytes have been reported to be present in the subfornical organ (Dellmann and Simpson, 1979; Dellmann, 1998). The GFAP positive astrocytes have been reported to express aquaporin-4 (Pócsai and Kálmán, 2015), endothelin (Gebke et al., 2000) and NaX, a subfamily of sodium channels (Hiyama et al., 2004). Based on the expression of these sodium channels, it has been suggested that a close communication between these glial cells and neurons may be involved in the control of salt homeostasis (Pócsai and Kálmán, 2015). The microglia/macrophages located in the parenchyma or in the perivascular spaces in the subfornical organ express MHC class I, MHC class II, CD4, CD45 and ED1 antigens (Pedersen et al., 1997). The presence of MHC antigens suggests that these cells are capable of antigen presentation to T lymphocytes and may serve as a first line of defense against infections in areas with a deficient blood-brain barrier (Pedersen et al., 1997).

The fenestrated capillaries are surrounded by relatively large perivascular spaces into which dendrites and axons project (Dellmann, 1998; Gross, 1991). The astrocyte end feet do not contact the capillary endothelium (Bouchaud et al., 1989). Occasional occurrence of capillaries without fenestrations and perivascular spaces similar to those found in the brain tissues has been reported (Dellmann, 1998).

### *Organum vasculosum of the lamina terminalis*

The OVLT is situated in the anterior wall of the third ventricle (Fig. 1A) in close vicinity of the median preoptic nucleus and approximately midway between the optic chiasma and anterior commissure. It is covered by the pia mater on the external surface and with ependyma on the ventricular surface. The ependyma consists of

typical ependymal cells and tanycytes, the processes which contact the perivascular spaces and the capillaries (Del Brio et al., 1990). Along with the subfornical organ, the OVLT is considered as a prime cerebral target for circulating ANG II and atrial natriuretic peptide to regulate body fluid homeostasis (McKinley et al., 1999). This is supported by the presence of high concentrations of angiotensin AT1 receptors in the OVLT (Allen et al., 2000). It is also considered as a site in the CNS that is responsive to circulating pyrogens to initiate a febrile response (Ott et al., 2010). It may also be involved in secretion of gonadotropin releasing hormone in mammals (McKinley et al., 2012).

Efferent connections of the OVLT are to the median preoptic, supraoptic and hypothalamic paraventricular nuclei whereas the afferent input comes from the subfornical organ and hypothalamic nuclei (Palkovits et al., 1977; Camacho and Phillips, 1981; Miselis, 1981; ter Horst and Luiten, 1986; McKinley et al., 2012). Glial cells such as astrocytes and microglial cells have been located in the OVLT and both cell types have been reported to be activated by cytokines such as TNF- $\alpha$  and IL-1 $\beta$  (Ott et al., 2010). However studies on detailed functions of these cells are lacking.

The vasculature of the OVLT is similar to the other circumventricular organs consisting of fenestrated capillaries surrounded by extensive perivascular spaces (McKinley et al., 2012). However, occurrence of some non-fenestrated capillaries surrounded by tanycyte processes has been reported (Krisch and Leonhardt, 1978).

### Dysfunction of the circumventricular organs and brain pathologies

Information on the pathology of circumventricular organs that may result in impairment of the brain function is limited. Involvement of dysfunctional circumventricular organs in brain pathologies such as stroke, neurodegenerative disorders, schizophrenia and neuroinflammation has been reported. Altered pineal gland volumes were suggested to be involved in the pathophysiology of schizophrenia (Sandyk and Kay, 1991; Fındıklı et al., 2015) and primary insomnia (Bumb et al., 2014). The involvement of the pineal gland in schizophrenia was further supported by the observation that nocturnal melatonin levels were significantly reduced in chronic schizophrenic patients (Ferrier et al., 1982). Pineal gland calcification has been suggested as a potential new contributor to several conditions such as cerebral infarction (Kitkhuandee et al., 2014), migraine (Ozlece et al., 2015), schizophrenia (Sandyk and Kay, 1991) and tardive dyskinesia (Sandyk, 1990). The occurrence of pineal cysts has been reported in patients with cerebral palsy (Özmen et al., 2015). Decreased production of melatonin from the pineal gland has been reported to be an underlying factor in the progression of several conditions such as multiple sclerosis and cataplexy (Sandyk, 1995) and Alzheimer's disease (Wu

and Swaab, 2005) among many others. The pineal gland, subcommissural organ, and organum vasculosum of the lamina terminalis have been reported as sites of origin of periventricular tumors (Szathmari et al., 2013). Endoplasmic stress in the subfornical organ was suggested to be a mediator of angiotensin-dependent hypertension as the organ is replete with ANG II receptors (Young et al., 2012). Defects in the subcommissural organ and its secretory activity have been implicated in the development of hydrocephalus (Pérez-Figares et al., 2001).

In sudden intrauterine and infant death syndromes related to maternal smoking, hypoplasia and cystic formations along with reactive gliosis in the area postrema of fetal brains were detected and it was suggested that the affected neurons in this organ involved in the control of vital functions may be the underlying cause of death (Lavezzi et al., 2012). Tumors of the neurohypophysis such as granular cell tumors (Lee et al., 2004) and pituicytomas presenting with reduced vision and headache (Chakraborti et al., 2013) have been reported.

### Conclusions

The circumventricular organs communicate with the CSF, serve as important links between the brain and the peripheral blood and mediate autonomic and endocrine functions under normal conditions. They are crucial in the maintenance of sodium and water balance, energy metabolism and cardiovascular regulation through their connections with the hypothalamus and the brainstem. They are also involved in immunomodulation as they are the sites where immune cells can enter into the brain and the CSF. The microglia/macrophages that are present in the perivascular spaces and the parenchyma of all the circumventricular organs serve as first line of defense to engulf and destroy the invading pathogens. However, prolonged activation of these cells may be involved in neuroinflammation in brain pathologies. Although investigations over many years have led to a better understanding of their physiological roles, more studies are warranted to explore their involvement in pathologies of the brain.

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## Circumventricular organs

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## Circumventricular organs

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