REVIEW

Sensory circumventricular organs in health and disease

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Abstract Circumventricular organs (CVOs) are specialized brain structures located around the third and fourth ventricles. They differ from the rest of the brain parenchyma in that they are highly vascularised areas that lack a blood–brain barrier. These neurohaemal organs are classified as "sensory", when they contain neurons that can receive chemical inputs from the bloodstream. This review focuses on the sensory CVOs to describe their unique structure, and their functional roles in the maintenance of body fluid homeostasis and cardiovascular regulation, and in the generation of central acute immune and febrile responses. In doing so, the main neural connections to visceral regulatory centres such as the hypothalamus, the medulla oblongata and the endocrine hypothalamic-pituitary axis, as well as some of the relevant chemical substances involved, are described. The CVOs are vulnerable to circulating pathogens and can be portals for their entry in the brain. This review highlights recent investigations that show that the CVOs and related structures are involved in pathological conditions such as sepsis, stress, trypanosomiasis, autoimmune encephalitis, systemic amyloidosis and prion infections, while detailed information on their role in other neurodegenerative diseases such as Alzheimer's disease or multiple sclerosis is lacking. It is concluded that studies of the CVOs and related structures may help in the early diagnosis and treatment of such disorders.

Sensory CVOs: cross-talkers between blood, cerebrospinal fluid and brain

It is barely a century since experiments demonstrated for the first time that there was some kind of compartmentalization between the central nervous system (CNS) and the bloodstream, the so-called blood–brain barrier (BBB). Ehrlich [38] and Goldmann [54] became the first to demonstrate that the CNS was the only organ which is not stained by dyes injected intravenously, and that it is stained only after intracerebral injection. The BBB is formed by capillary endothelial cells joined together by tight junctions, their basal membrane, and surrounding pericytes, astrocytic end-feet, and microglial and neuronal processes [1, 102]. This barrier effectively segregates the CNS from the periphery, ensuring that neurotransmitters, neuromodulators, neuropeptides and growth factors do not diffuse out of the CNS into the circulation, and that blood-borne endocrine hormones, pathogens and cytokines, amongst others, are prevented from entering the CNS [102].

Despite this barrier, CNS regulatory centres are able to respond to changes in the level or concentration of circulating molecules, solutes or toxic substances in order to maintain the "*milieu intérieur*" (homeostasis). Early experiments by Wislocki et al. [155] and by Behnsen [13] demonstrated that minute structures in the CNS were stained with intravenously administered dyes indicating that they lacked a BBB [154]. In 1958, it was found that those neurohaemal structures were located around the ventricles, and were accordingly named circumventricular

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organs (CVOs; [65]). The CVOs can be traced by intravenous injection with horseradish peroxidase [16] or examined in vivo by fluorescence endoscopy [79]. Later on, CVOs were called the "windows of the brain" [59] because of their distinct neurohaemal morphological features, such as their capillaries being fenestrated and glial cells being more loosely apposed, creating relatively large perivascular spaces. In consequence, large molecules and polar substances can readily pass to and from the blood to the perivascular spaces exposing neurons to peripheral signals [39].

According to recent opinions, there are eight CVOs: three sensory, four secretory and one that is unclassified [25]. The sensory CVOs include the subfornical organ (SFO), the organum vasculosum of the lamina terminalis (OVLT) and the area postrema (AP). The secretory CVOs are the neurohypophysis, the median eminence, the pineal gland and the subcommisural organ. The choroid plexus is occasionally considered as a CVO because of its fenestrated capillaries but it lacks any neural tissue, while the subcommisural organ is often disregarded as a CVO because it does not have fenestrated capillaries [108].

Circumventricular organs (CVOs) have been regarded as likely points of communication between the blood, the cerebrospinal fluid (CSF) and the brain parenchyma [69, 92]. Eight classes of interactions between these three compartments have been proposed considering both signal source and target, and mode of information transfer (hormonal, neural or humoral [69]). Sensory CVOs mainly act as class II and class III CVOs [69]. By definition, class II CVOs contain both neuronal soma and terminals [57] to sample molecules from blood and interstitial fluid. Subsequently, these neurons will transfer information via neural connections (Class III) to distant brain structures that have a BBB.

Functionally, the CVOs help in maintaining homeostasis through regulation of movement of solutes and chemicals from the circulatory system into the brain parenchyma and vice versa, and respond immunologically to inflammatory cells or to infectious agents that circulate in the bloodstream. The sensory CVO neurons in turn innervate major neural effector centres for most autonomic functions, for maintaining body fluid homeostasis, and for initiating immune responses.

The present review focuses on the sensory CVOs with the main aims of (i) describing their unique characteristics as neurohaemal organs, (ii) showing that—as a dynamic system—they are capable of responding to peripheral and local changes and requirements, (iii) describing their ability to regulate a number of mechanisms in physiological and pathological conditions, (iv) pointing out their possible roles as portals of entry and distributors of some infectious agents that can affect animals and humans, and (v) formulating the hypothesis that disruption of these organs

might be critical in the initiation, development and progression of some neurological diseases.

Vascular architecture and neuroanatomy

Although with some slight differences depending on the species (reviewed in [91]), the mammalian sensory CVOs receive blood supply through branches of the anterior cerebral (OVLT and SFO) and of the cerebellar (AP) arteries. These arteries branch into extensive networks of primary capillary plexuses arising from intrapial vessels, which can be twisted and looped as secondary capillaries when entering subependymal regions [35, 36]. Those capillary plexuses drain into veins usually located within the CVOs themselves and occasionally in the brain parenchyma, like in the case of the OVLT that drains into the preoptic region [20]. A recent atlas highlights some of the differences in the vascular architecture within the CVOs between humans and non-human species [37].

Capillaries within the CVOs differ in type according to the continuity of the endothelial sheath, the number of intracellular vesicles, the lumen diameter, the endothelial wall thickness and the size of the peri-capillary space [58, 124–126]. Dellmann [31] described three different types of capillaries that can be found in the CVOs. Type I capillaries have a continuous, non-fenestrated endothelium but differ from the typical CNS capillaries in that they have relatively larger perivascular spaces and abundant vesicles within the endothelial cells. Type II capillaries possess the same characteristics as those of the rest of the CNS, while type III capillaries differ fundamentally from those of the brain parenchyma. Type III is the most permeable capillary type as, in addition to the endothelial fenestrations, their endothelial cells have many intracellular vesicles and pits, their walls are thin, their luminal diameter is large, and their perivascular spaces are dilated containing neuroglia elements [31]. In addition, basement membranes surrounding the perivascular sheaths contain neurons, axon terminals, collagenous fibrils, macrophages and fibroblasts, but not astrocytes.

In coronal sections, the lamina terminalis, historically called supraoptic crest, forms a sagittal fold above the optic chiasm as part of the supraoptic recess of the third ventricle [37]. Two of the sensory CVOs are part of this structure: the OVLT and the SFO (Fig. 1).

The OVLT, which is the vascular organ of the lamina terminalis, is a thin structure fixed in the anterioventral border of the optic chiasm that forms the anterior wall of the third ventricle. The vascular architecture of the OVLT is similar to that of the median eminence in the sense that it is formed by two primary capillary networks (a superficial intrapial plexus and a deeper outer plexus) and a secondary
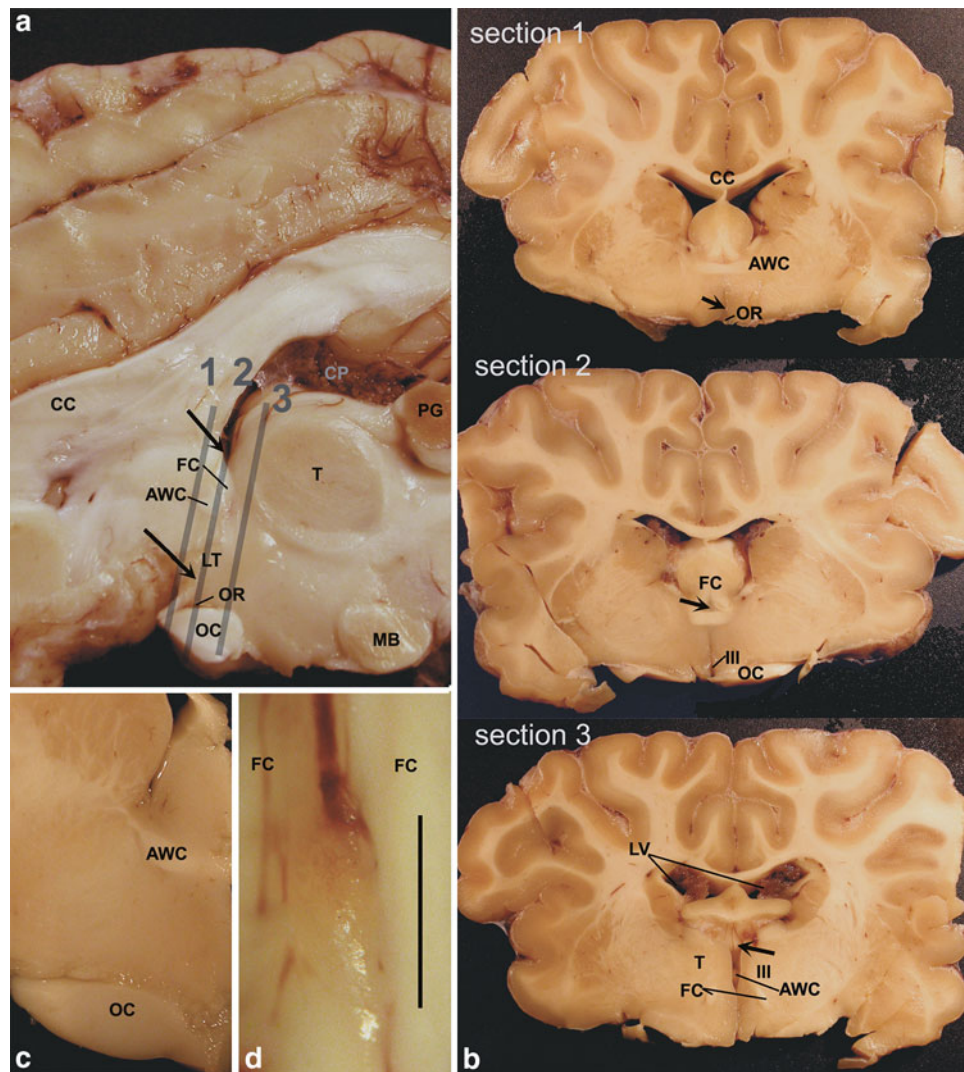
Fig. 1 Neuroanatomical location of the SFO and the OVLT in the sheep brain. **a** Sagittal section of the diencephalon indicating the locations of the CVOs (*arrows*) associated with the *lamina terminalis* (*LT*) and the three levels of trimming (1, 2 and 3) for their optimal visualisation. **b** Transversal sections obtained from Sections 1, 2 and 3. *Section 1* shows the most anterior part of the OVLT (*arrow*) ventral to the anterior white commissure (AWC) and dorsal to the optic recess (*OR*). Note that the third ventricle (III) is not represented in this section. *Section 2* shows the most anterior part of the SFO (*arrow*) between the columns of the fornix (*FC*) and dorsal to the AWC. Note that the ventral opening of the III is represented in this section. *Section 3* shows the posterior part of the SFO (*arrow*) at the dorsal opening of the III. **c** The OVLT grossly has a gelatinous appearance and it is found dorsomedial to the optic chiasm (*OC*). **d** Grossly, the SFO is translucent in appearance and highly vascularised. In sheep, the SFO is quite prominent and protrudes towards the communication between the III and the lateral ventricles (*LV*). *Bar* 0.2 mm. *CC* corpus callosum, *CP* choroids plexus, *PG* pineal gland, *T* thalamus, *OC* optic chiasm, *MB* mammillary body

capillary plexus [124]. The intrapial plexus connects with the subarachnoidal space at the prechiasmatic cistern, whereas the secondary capillary plexus is limited to a subependymal network of looping capillaries that connects with the third ventricle (Fig. 2a). In humans, such a capillary network forms a ring with the loops oriented towards the centre of the ring [37]. Only the deep plexus has fenestrated capillaries [76] except in the rat, in which endothelial tight junctions are found in all capillaries of the OVLT [108]. Processes of meningeal cells and tanycytes separate the periventricular compartment, which contains the fenestrated secondary vascular plexus and subependymal capillary loops, from the superficial intrapial compartment. These processes may form a perivascular double basal membrane [122].

The SFO, previously named *ganglion psalterii* [134] or intercolumnar tubercle [114], is on the midline rostral wall of the third ventricle in the dorsal region of the lamina terminalis, ventral to the origins of the columns of the fornix and dorsal to the anterior white commissure ([32];

Fig. 1). In humans, it protrudes slightly into the intersection point between the lateral and the third ventricles at the confluence of the foramen of Monro [3, 37, 114]. The most superficial capillaries are seen on an endo-ventricular view [37]. The posterioventral surface of the SFO is in contact with the pial connective tissue of the choroid plexus through a continuous layer of glial processes ([58]; Fig. 2c). In the rat SFO, there is an outer dorsal shell and an inner ventromedial core (Fig. 2c); it is the inner core that contains the dense networks of type III capillaries [31, 126].

The AP is attached to the ventral angle of the floor of the fourth ventricle at its opening to the central canal at the level of the obex. It consists of two lateral masses in humans and most mammals, but a single median mass in rodents and lagomorphs. The dorsolateral part of the AP is attached to the tela choroidea, and in humans is connected with the subarachnoidal medullo-cerebellar cistern. The gross morphology of the AP is different from the adjacent vagal complex nuclei in that it is a highly vascularised structure (Fig. 3a) composed of large and sinusoidal capillaries [97]. Similar to the OVLT, a layer of tanycytes representing the *funiculus separans* provides a barrier with adjacent structures that contain a BBB, like the solitary tract nucleus (STN [76]). It is uniformly composed of a network of numerous subependymal loops of anastomosed large-calibre type III capillaries. Electron microscopy studies in the 20th century revealed double subendothelial basement membranes between which electron dense particles were trapped [33, 146].

As mentioned earlier, the vascular architecture of the OVLT is similar to that of the median eminence but different from that of the SFO and AP. Recent investigations showed that the fenestrated capillaries of the SFO and AP, but not those of the OVLT, can express type 1 aquaporin water channels [153]. Gross [58] observed that the plasma flow and blood-to-tissue transfer was increased in the capillaries of the SFO and AP compared to adjacent brain structures, and that the blood flow within those CVO capillaries was slower than in those of the rest of the brain. They concluded that this would allow plasma to gain better access to the receptors of those sensory CVOs.

The SFO and AP are located in close proximity to ventricular junctions, and the OVLT to ventricular recesses. At those sites, the ependymal lining contains specialized ependymocytes and tanycytes. Ependymocytes are linked by tight junctions that establish a barrier between the CSF and the brain [37, 91]. In contrast, tanycytes have multiple processes (microvilli or cilia) that contact with the CSF and extend into the body of the CVOs [57]. By linking the CSF and CVO environments, tanycytes could provide a functional role for the CVOs to monitor the composition of the CSF [37, 98]. Goren et al. [56] defined the CVOs as

Fig. 2 Drawings of the vasculature, anatomical subdivisions and main efferent connections of the sensory CVOs in a lateral view (**a, c, e**) and a transversal front view (**b, d, f**). **a** The vascular architecture of the OVLT contains rostrally two capillary networks originating from the anterior communicating artery (*ACA*) and the preoptic artery branches (*PO*): the superficial intrapial primary plexus (*yellow background*) and the deep outer primary capillary plexus with capillary loops (*orange background*). The anterior limit of the OVLT is separated by meninges (*thick black line*) at its proximity with the prechiasmatic cistern. The deep outer capillary plexus which is continuous with the secondary capillary plexus has fenestrated capillaries. The secondary capillary plexus is located in the periventricular area in contact with the ependyma of the 3rd ventricle (III). The posterior thick wall represents the specialized ependyma of this CVO. Blood drains into branches of the PO vein. **b** The three main subdivisions of the OVLT are shown in different colours. The anterior vascular inner region is surrounded dorsally by the dorsal cap and by the lateroposterior zone both of which maintain connections mainly with hypothalamic nuclei. **c** The ventromedial core of the SFO has the most dense fenestrated vascular architecture and contains the specialized ependyma (*thick wall*). They arise from branches of the preoptic artery and drain into vein branches. **d** Most efferent hypothalamic connections leave from the outer shell, as shown in the posterior transversal view. **e** The vasculature of the AP arises from the cerebellar artery (*red*) and branches into tortuous capillary networks in the periventricular zone, which is in contact with the fourth ventricle (IV). Blood is drained into vein branches (*blue*) that run ventrally along the ventral zone. **f** Most efferent connections are originated in intermedio-ventral areas of the AP and terminate in adrenergic cell centres. The ventral junctional zone is in contact with the solitary tract nucleus (*STN*). Note that afferent nerve input from the vagus and glossopharyngeal nerves terminate in the periventricular medial zone. *SON* supraoptic nucleus, *PVNm* magnocellular part of the paraventricular nucleus, *PVNp* parvacellular part of the paraventricular nucleus, *BNST* bed nucleus of the stria terminalis, *Lat HT* lateral hypothalamic nucleus, *OR* optic recess, *OC* optic chiasm, *PBN* parabrachial nuclei, *MnPO* median preoptic area, *LV-III* intersection between lateral and III ventricles, *NA* nucleus ambiguous, *VLM* ventrolateral medulla

"hypendymal organs" because they possess glial and vascular plexuses, no BBB, and high aquaporin-4 expression. In contrast, the so-called "ependymal organs" of the brain do have a BBB and a thickened and pseudostratified ependyma immuno-negative for aquaporin-4 [56].

Roles of the sensory CVOs in health: regulators of endocrine and integrated autonomic functions through the CNS

Most anatomical studies describing the projections to and from the CVOs have been conducted in rats and using tracing methods further validated by electrophysiological techniques [42]. The OVLT, SFO and AP are integrated in CNS circuits which connect them mainly with the autonomic regulatory centres of the CNS, the hypothalamus and the dorsal vagal complex [25].

Many different anatomical subdivisions have been proposed for the sensory CVOs (as reviewed by McKinley et al.
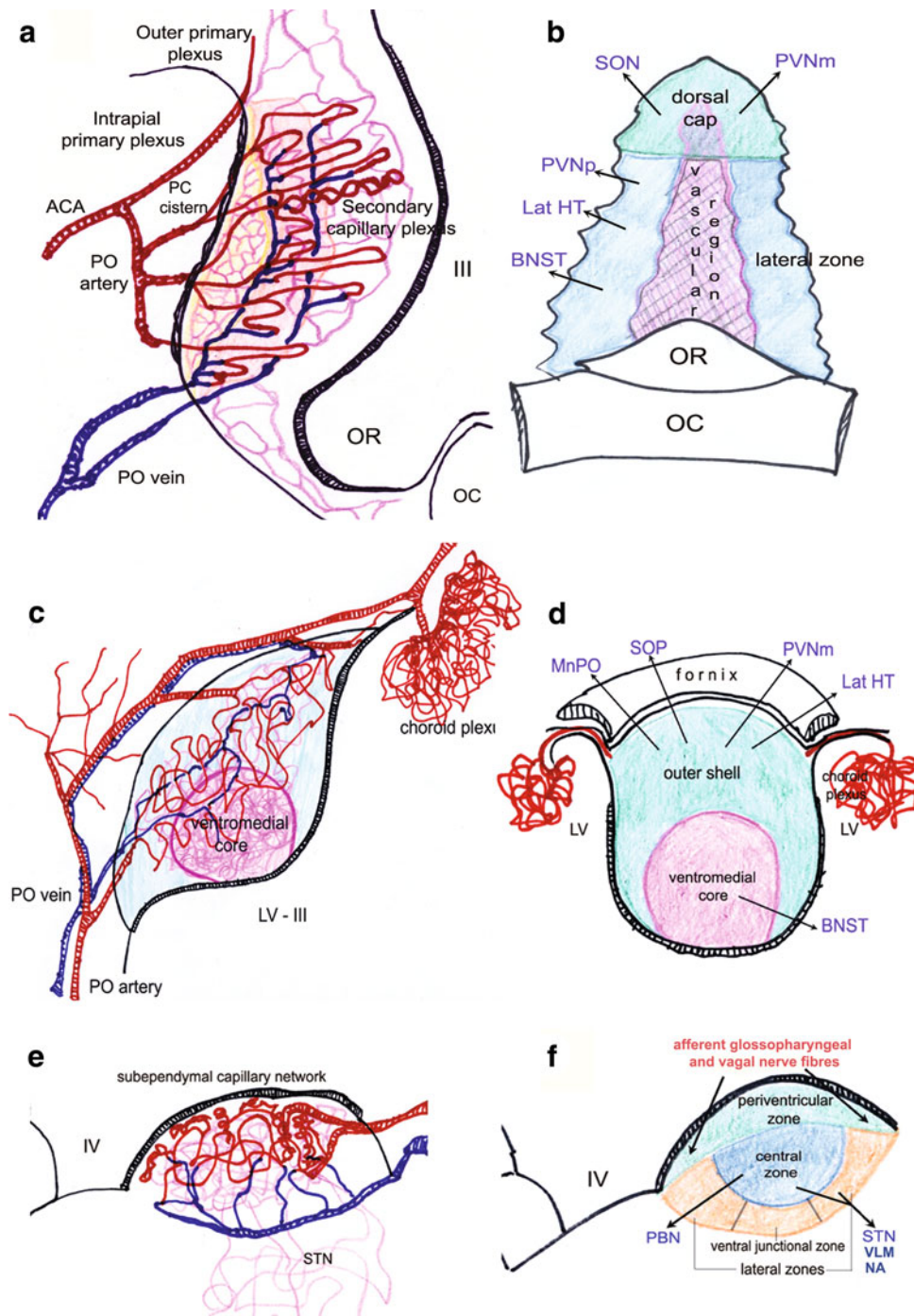
[91] and Dellmann [31]). Drawings in Fig. 2 reproduce those subdivisions as given by McKinley et al. [91] from a functional point of view, but also depict the main neural connections as proposed by several authors [25, 69, 91].

Neural architecture of the sensory CVOs

Three main functional subdivisions of the rat OVLT are proposed: an arching dorsal cap, a ventrorostral inner vascular region, and two ventrolateral areas that converge in the posterior aspect of the organ in close apposition to the ependyma of the third ventricle (Fig. 2b). In humans, the rostral part of the vascular region is devoid of neuronal perikarya and is composed largely of astrocytic processes, basement membranes and perivascular spaces of the intrapial primary plexus. The dorsal cap provides the major source of efferent connections to the supraoptic nucleus [89, 99, 109, 136], to magnocellular neurons of the

Fig. 3 Macro- and microscopical appearance of the ovine AP. The distribution of the rich vasculature is more homogenous throughout this CVO (**a**). The AP contains high numbers of neuronal somas, as denoted by positive immunolabelling with neuronal nuclei (*NeuN*) antibodies in the central zone (**b**). It is very well interconnected with the vagal complex, as shown by strong synaptophysin immunolabelling (**c**), in comparison to neighbouring structures like the solitary tract nucleus (*STN*) and the dorsal motor nucleus of the vagus nerve (*DMNV*). *STT* solitary tract, *XII* hypoglossal nucleus. Distinctly from vagal complex structures, the AP shows strong immunoreactivity against paravalbumin (**d**). Immunolabelling for microglial cells/macrophages with coronin-1 shows differences in numbers of positive microglia resident cells between the AP of a healthy sheep (**e**) and activated mononuclear cells in a case of a non-purulent encephalitis in sheep (**f**). **b**, **e**: ×10; **c**, **d**: ×2; **f**: ×20
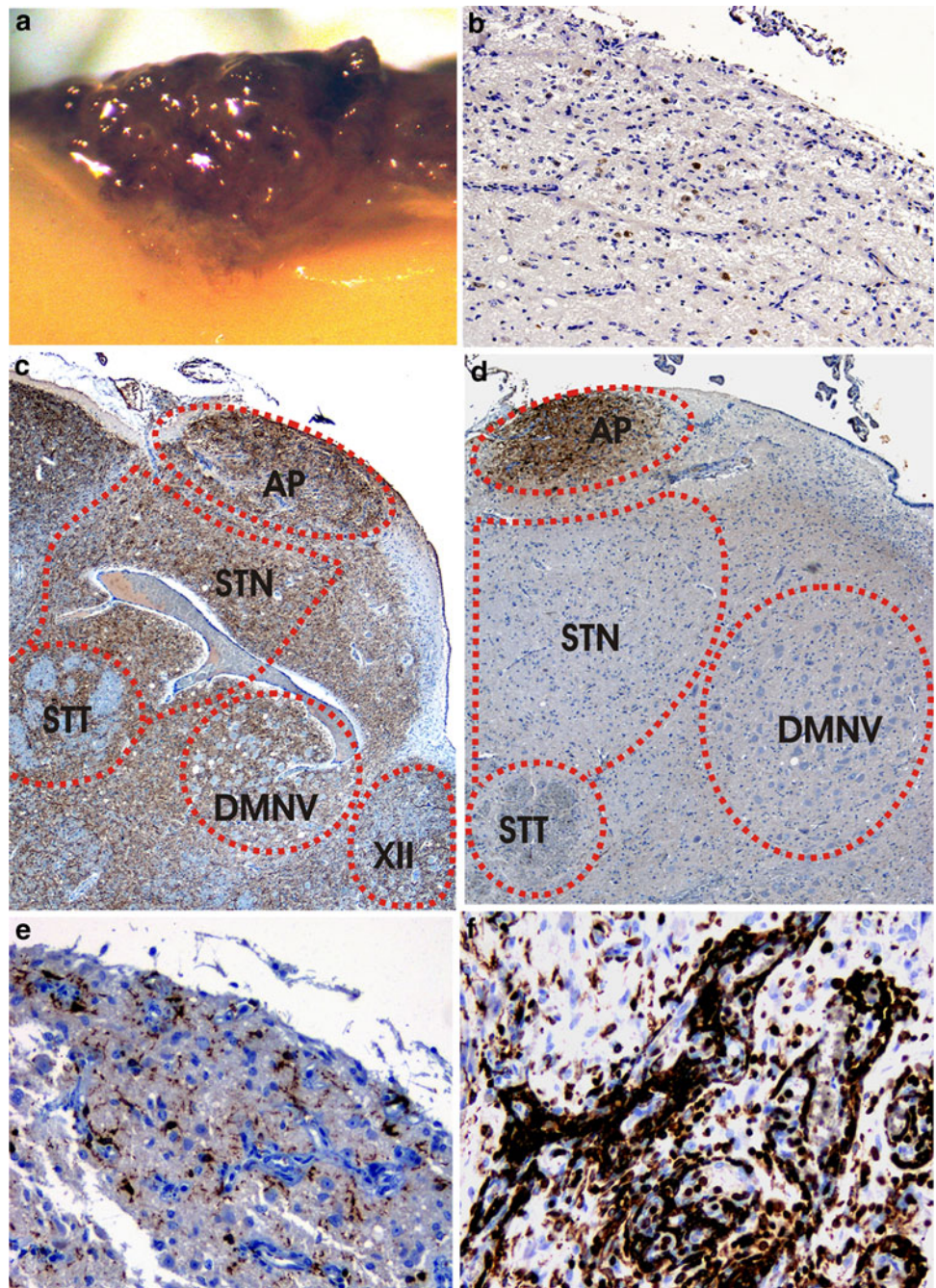
paraventricular nucleus [60, 136, 145] and to the cerebral cortex [91]. Neural projections leave the lateral-periventricular subdivision to connect with the lateral hypothalamic area, the bed nucleus of the stria terminalis and the parvocellular neurons of the paraventricular nucleus [136, 145]. Terminal fields of those projections are found in limbic structures such as the septal area, hippocampus and cingulate cortex [18], in midbrain areas such as the periaqueductal grey matter, lateral parabrachial nucleus and locus coeruleus [18, 60], and in the medullary raphe nucleus [145].

Moreover, experimental data using viral tracers have revealed polysynaptic efferent pathways originating in the dorsal cap and lateral areas of the OVLT connecting with neurons of the hypothalamic paraventricular nuclei and ending in peripheral organs such as the kidney (for details see [91]). Neurons in the OVLT also send and receive projections from the two other components of the lamina terminalis, the SFO and the median preoptic nucleus in rats [18, 60, 100] and in sheep [101], and may receive neural input from the nucleus of the solitary tract [25]. Minor

connections with other hypothalamic nuclei (ventromedial, arcuate, medial preoptic, anterior and posterior nuclei) have also been described [18].

In the rat SFO, there is an outer dorsal shell and an inner ventromedial core (Fig. 2c, d). According to morphological studies, both subdivisions contain numerous neurons, but it is the inner core that contains the largest number of neuronal somas and afferent nerve terminals [31]. The outer shell is the origin of almost all efferent fibre projections towards hypothalamic nuclei ([142]; Fig. 2d). The median preoptic area is one of the major efferent targets of the SFO in rats [84, 94] and sheep [90, 91, 101]. Fibres leaving the SFO travel mainly through its ventral stalk into the adjacent median preoptic area or into the columns of the fornix to project directly or indirectly towards the OVLT, paraventricular and supraoptic nuclei [84, 91, 95, 141], suprachiasmatic nuclei [91, 100] and ventrolateral medulla [74]. Neurons of the outer shell project to the infra-limbic part of the pre-frontal cortex, to the substantia innominata (ventral pallidum), to parts of the zona incerta, and to the lateral hypothalamus [94, 96, 140], whereas those of the ventromedial core project to the bed nucleus of the stria terminalis [140] with efferent terminal fields found in the midbrain raphe [83]. Similar to the OVLT, STN projects laterally to the SFO. The outer shell of the SFO has polysynaptic pathways to sympathetic and parasympathetic nerves that supply peripheral organs and tissues such as the kidney, adrenal gland, heart and gut [91].

Gross [58] proposed that the AP was divided into three main divisions: a dorsal periventricular mantle zone, a half-moon shaped central zone, and a ventrolateral zone containing the ventral junctional zone adjacent to the STN (Fig. 2f). The AP forms the vagal complex together with the STN and the dorsal motor nucleus of the vagus nerve (DMNV; Fig. 3c, d). Fewer neurons, but many glial cells are found in the ventral zone of the AP next to its boundaries with the STN ([106]; Fig 3b, e). Efferent pathways from the central and lateral zones project first to the adjacent solitary tract, and ventrolaterally to the A1 noradrenergic group, and to the nucleus ambiguous (Fig. 2f), where some monosynaptic axons terminate [123]. Alternatively, they relay on the lateral parabrachial nucleus to further terminate in the ventrolateral aspect of the periaqueductal grey matter and in the mesencephalic nucleus of the trigeminal nerve [123], the dorsal tegmental nucleus [148], and unspecified parts of the cerebellar vermis [123]. A similar polysynaptic pathway from the AP to the suprachiasmatic nucleus has been identified [78]. In the rat, according to Cunningham et al. [27], the DMNV receives few if any fibres from the AP. Most afferent projections terminating in the AP originate in the parvocellular group of neurons of the paraventricular nucleus and in neurons of the dorsomedial nucleus of the

Table 1 Some of the receptors and binding sites identified in sensory CVOs [91]

Receptor and binding sites	SFO	OVLT	AP
Angiotensin II AT_1	+++	+++	+++
Glutamate NMDA or AMPA	+++	+++	+++
Glucocorticoid	++	++	++
Receptors for lipopolysaccharides	+++	+++	+++
Neurokinin R (subst P)			+
Prostaglandins R (EP2, EP3, EP4)	+++	+++	+++
Neuropeptide Y	+++		+
ATP purinergic R			+
Vasopressin V1	+++		+++

hypothalamus and perifornical region [123], STN and the lateral parabrachial nucleus. Unlike those CVOs related to the lamina terminalis, the AP receives direct innervation from visceral nerves through sensory components of the vagus and glossopharyngeal nerves, which terminate in the dorsal periventricular mantle ([71, 91]; Fig. 2f), conveying information from the abdomen and thorax [21, 23, 24, 71, 72, 111], and from the kidney [132].

CVOs as neurochemical sensors and transducers

Autoradiographic binding studies, in situ hybridisation and immunohistochemistry have revealed that sensory CVO neurons or fibres contain hormones, neurotransmitters, neuropeptides and enzymes. These neurons act as neurochemical sensors for blood-borne stimuli, through synaptic input (through axonal terminals) or by coupling to receptors.

When extracellular ligands such as hormones or neurotransmitters, which act as the "first messenger", bind to different receptors, usually transmembrane proteins [91, 111], they in turn activate intracellular protein effector responses named "second messenger". These second messengers act as transducers leading to increased levels of intracellular calcium. Subsequently, gene expression of transcriptional factors is increased. Table 1 provides a partial overview of some receptors that are discretely localized in the CVOs, as reported by McKinley et al. [91].

Large numbers of investigations on early gene expression have provided the main bulk of knowledge on the functional roles of the sensory CVOs. These studies are based on the examination of the distribution of activated neurons by means of the expression of the gene transcription factor c-Fos in response to blood-borne stimuli. Some examples found in the literature include, (i) increased c-Fos expression in the OVLT and SFO after infusion of hypertonic solutions, after induction of sodium depletion or dehydration, or as a result of increased levels

of circulating angiotensin II, suggesting that these CVOs can be responsible for maintaining the water and electrolyte balance, (ii) increased c-Fos expression in the AP after elevated arterial pressure and after infusion of anorectic peptides or emetic stimulation, implying that this CVO influences somewhat the cardiovascular function and appetite, and (iii) increased c-Fos expression in the CVOs after parenteral injections with bacterial endotoxin lipopolysaccharides (LPS) or after interleukin-1 (IL-1) administration, suggesting that CVOs might be responsible for fever and immune responses.

Gross [57] proposed some CVO functions in the maintenance of body fluid balance, blood pressure, temperature, respiration, energy balance, mediation of immune responses, pain modulation, protection against ingested toxic substances, biological rhythms, reproduction, parental behaviour, lactation, growth, sleep, arousal and attention. Our understanding of the prominent role of the CVOs has advanced in these past two decades and extensive reviews on some of the specific functions of the CVOs are available [25, 34, 47, 49, 63, 69, 91, 135]. Herein, we focus on their direct role in the regulation of body fluid homeostasis and cardiovascular function and in the stimulation of autonomic regulatory centres of the CNS.

Physiological role of CVOs in the maintenance of body fluid homeostasis

Body fluid homeostasis is disturbed in the face of water and/or sodium deficiency or excess. The renin–angiotensin system is classically considered as an endocrine mediator in the regulation of the cardiovascular function, with angiotensin II affecting vascular tone, and stimulating water and sodium reabsorption by the kidney when low water and sodium levels are present in blood. In addition, angiotensin (I and II) can act centrally through initial signalling into sensory CVOs influencing (i) drinking behaviour, (ii) neuroendocrine secretion of adrenocorticotropic, oxytocin and vasopressin hormones, and (iii) autonomic control of the cardiovascular function via sympathetic efferences. Conversely, when water and sodium ion levels are high, the opposite orchestration—the pattern of the behavioural, cardiovascular and renal responses—will take place.

Water deprivation, hyponatremia or blood-borne angiotensin I or II activate osmoreceptors in neurons of the OVLT [67, 115, 151] and SFO [7, 62]. Calretinin- or calbindin-expressing neurons in the OVLT and neurons of the SFO are rich in angiotensin II type 1 receptors and angiotensin-converting enzyme [6, 52, 91, 133]. Their c-Fos expressing neurons will in turn, via previously mentioned connections, stimulate salt and water-intake behaviour [46]. Efferent stimulations towards neurons in the A3V3 region, in the supraoptic nucleus and magnocellular neurons of the paraventricular nucleus, which are known to be the source of vasopressin and oxytocin [43–45, 66, 129], will direct such response by releasing those hormones to the posterior lobe of the pituitary gland. In addition, the SFO transduces the signal to parvocellular neurons of the paraventricular nucleus, with the ensuing release of corticotrophin-related hormones from the anterior pituitary gland. Simultaneously, hypothalamic responses will activate sympathetic outflow regulatory autonomic centres located in the medulla oblongata that react to oxytocin, vasopressin or corticotropin-releasing factor. Subsequently, neurons in the intermediolateral column of the spinal cord and sympathetic ganglia are stimulated [22, 84]. Figure 4 shows the presence of oxytocin in axons and in neurons of the CVOs of the lamina terminalis and the hypothalamic nuclei, respectively.

Circulating angiotensin II concurrently stimulates the AP directly, which in turn activates the sympathetic regulatory centres such as the STN, and the ventrolateral medulla in order to increase blood pressure or reset the baroreceptor reflex, respectively [91]. Angiotensin II type 1 receptors are uniformly present in the AP [6], which is the only sensory CVO that contains an A2 noradrenergic subpopulation of catecholamine- or serotonin-containing neurons [91] and the highest numbers of neurons exhibiting GABA neurotransmitters (Fig. 3d). This stimulation produces vasoconstriction, thus regulating arterial pressure and cardiovascular function. This effect is balanced by the baroreceptor reflex that vasopressin, atrial natriuretic peptides and endothelin produce by acting on neurons of the AP [15, 19, 61, 70, 144]. The influence of the OVLT on blood pressure is believed to be mediated by its intimate connections with the preoptic area [64, 86]. In addition, Giles et al. [52] suggested that polysynaptic input generated by neurons in the SFO and in the OVLT might influence the sympathetic supply to the kidney and to the adrenal medulla.

The knowledge of these orchestrating events in health can provide the basis for some therapeutical strategies in disease. Alzheimer's disease (AD) is characterized by dementia in association with deterioration of the cardiovascular system. Pharmacotherapy targeting the renin–angiotensin system, especially that using angiotensin blockers rather than angiotensin-converting enzyme inhibitors is one of the most effective means of reducing hypertension and cardiovascular morbidity [81]. In the following sections, we will discuss the role of CVOs in disease.

Role of sensory CVOs in inflammatory diseases

In health, CVOs are cross-talkers between the immune, the endocrine and the nervous systems in order to maintain homeostasis. If we consider that inflammation alters

Fig. 4 Oxytocin immunoreactivity in the sheep OVLT and SFO and their main connecting nuclei, the paraventricular and supraoptic. **a** Strong oxytocin-containing fibres can be observed in the anterior part of the OVLT (*encircled*), which is mainly composed of astrocytes and basement membranes of the primary capillary plexus. *OC* optic chiasm. In contrast, its dorsal cap (**b**) shows low numbers of positive neurites (*arrows*), similar to its neighbouring median preoptic nucleus (*MNPO*). **c** The SFO also shows strong immunoreactivity for oxytocin in the area of the superficial capillary plexus in the outer zone and weaker in the ventromedial core (*framed*). Note the strong immunolabelling in the perifornical area surrounding the branches of the preoptic artery (*POA*). The fewer oxytocin-containing fibres of the ventromedial core are better appreciated at higher magnification (**d**). Both the OVLT and the SFO stimulate the synthesis of oxytocin by the magnocellular neurons of the paraventricular nucleus (*PVN*; **e**) and by neurons of the supraoptic nucleus (*SON*; **f**). *FC* fornix columns, *PFN* perifornical nucleus. **a**: ×2; **b**: ×20; **c**: ×10; **d**, **e**: x4
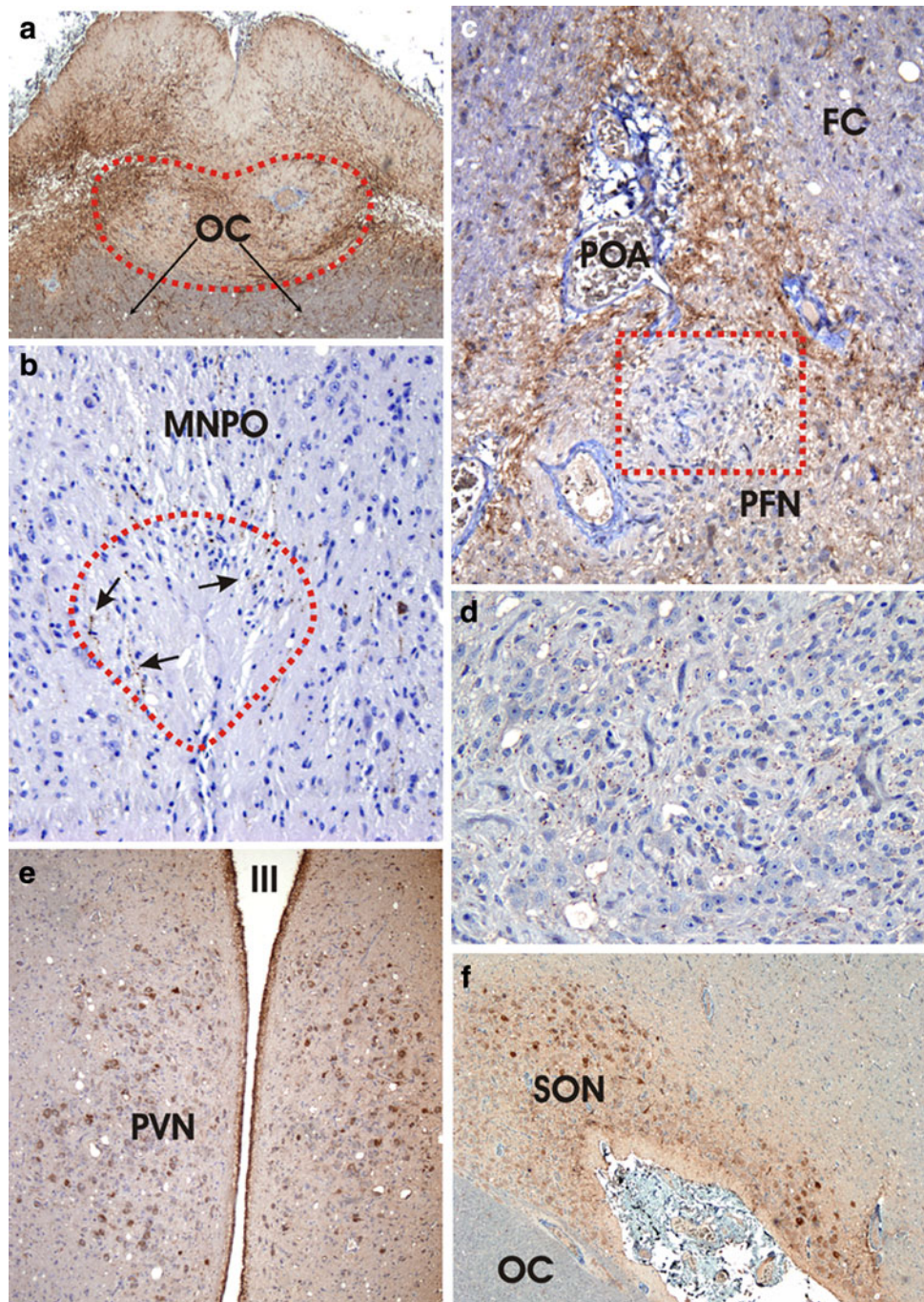
homeostasis, then we could anticipate that the CVOs might have a role in inflammatory diseases. In this section, we will describe some known roles of the CVOs such as (i) portals of entry for circulating infectious agents, immunogenic peptides or inflammatory cells, (ii) transduction sites for the activation of the regulatory sites to control the immune response and fever, and (iii) contributors to sickness behaviour.

CVOs are portals for infectious agents to entry into the brain

Most infectious agents can reach the CNS via peripheral nerves or via blood, or by a combination of both as has been recently suggested in animal prion diseases (see section below). Similarly, the immune response to peripheral infections can reach the CNS either through

visceral sensory afferent fibres, or via the blood through the CVOs or crossing the BBB [17, 29, 30, 152]. A few investigations have explored the involvement of the CVOs in the neuroinvasion process for some infectious diseases.

Human African trypanosomiasis, also known as sleeping sickness, is caused by extracellular *Trypanosoma* spp. parasites. This disease is characterized by severe disturbances in regulatory functions of the CNS such as disruption of sleep–wake rhythms, hormonal secretion, or body temperature. Recent evidence suggests that the CVOs act as portals of entry for circulating parasites [121] and elicit the central immune response [77]. This response leads to the production of pro-inflammatory cytokines like interleukin-1β (IL-1β), tumour necrosis factor-α (TNF-α), interferon-γ and inducible nitric oxide synthase [77]. Subsequent spread of the inflammatory process to adjacent limbic brain areas causes pathology and clinical symptoms [77].

The CVOs have also been reported to play a role in the recruitment of inflammatory cells into the brain. In experiments in rats with experimental autoimmune encephalomyelitis (EAE), the animal model for multiple sclerosis, immune cells migrate from the blood into the CNS and CSF overcoming the BBB. Schulz et al. [120] examined the role of the CVOs in this model and found that during clinical stages of EAE, there was an increase of CD45+ leukocytes and an up-regulation of the adhesion molecules ICAM-1 and VCAM-1 in the fenestrated capillaries of the CVOs, with presence of cells positive for MHC class I and class II antigens in the perivascular spaces. They found that these inflammatory changes were more severe in the CVOs than in neighbouring brain areas, suggesting that the CVOs could be the sites of entry of inflammatory cells into the CNS. CVOs from rats with systemic immunological disorders such as systemic lupus erythematosus or systemic amyloidosis showed protein deposits in the fenestrated vessels [107, 128].

CVOs role in stress: transduction sites for fever and activation of the hypothalamic-pituitary axis (HPA)

Stress can be defined as an anticipated threat to well-being and a disruption of homeostasis [143]. Despite the CNS being considered an immunologically privileged site, it is well known now that the brain and the CVOs monitor peripheral innate immune responses [48]. Ageing itself is associated with increased pro-inflammatory activity in the brain. In this section, we will describe the mechanisms by which the CNS interconnects with the periphery in order to balance the pro- and anti-inflammatory response.

There are two main pathways by which the immune system communicates with the brain in order to activate the HPA: a neural pathway and a humoral pathway [17, 29, 30, 152]. Briefly, the neural pathway is characterized by immune stimulation of visceral sensory afferent fibres of the sub-diaphragmatic vagus nerve that relay in the STN [30]. The humoral pathway involves the Toll-like receptors on macrophage-like cells residing in the CVOs and the choroid plexus [30, 152]. The parallelism or convergence of both pathways in target brain areas is unclear at present [29]. For example, is fever the result of pyrogenic cytokines in the hypothalamus being stimulated by prostaglandin E$_2$ (PGE$_2$) production in the CVOs (humoral hypothesis)? Or is the liver production of PGE$_2$ mediated by LPS and complement component C5a which stimulates the hypothalamus via the vagus nerve (neural hypothesis)? [137, 138]. As part of the humoral response, endothelial and microglial cells of the CVOs are activated (Fig. 3e, f) and secrete pro-inflammatory cytokines such as IFN-γ, TNF-α and PGE$_2$ [41, 73, 118, 137, 147]. Such cytokines may pass from the CVOs into the brain by diffusion and activate the febril response indirectly by acting on the preoptic area of the hypothalamus, the area that regulates the body temperature [30, 116, 138, 142]. This acute-phase response with IL-1β and TNF-α results in the development of "sickness" behaviour such as decreased appetite, altered sleep/wake cycles and changes in the neuroendocrine system [17, 28, 30].

The activation of the HPA in stress, which is a multi-step process [17], is the most important neuroendocrine disturbance associated with inflammation [80]. Initial circulating cytokines activate prostaglandin production in the CVOs and by catecholaminergic cell groups of the ventrolateral medulla and STN [17]. Subsequently, paraventricular neurons that contain corticotrophin-releasing hormone (CRH) and vasopressin are stimulated. In turn, they activate the release of adrenocorticotropic hormone (ACTH) from the anterior pituitary, and the ACTH stimulates the production of cortisol from the adrenal cortex increasing cortisol levels in plasma. This last effect has a negative feedback towards the stimulation of the HPA [17] in an attempt to protect the organism against the potentially toxic effects of cytokines after they have produced their initial beneficial effects. If this dampening does not take place, animals or humans will die. Sepsis-associated encephalopathy is a neurological syndrome that reflects an uncontrolled systemic inflammatory response to a source of infection [5, 8]. In sepsis, the concomitant expressions of IL-1β and the inducible isoform of nitric oxide have been demonstrated in the CVOs and related structures [75]. These neurotoxic effectors have a detrimental inhibitory effect on the central production and release of hormones, thus impairing the restoration of homeostasis due to stress [5, 17].

The role of CVOs in patients with depression has not been explored in depth. Evidence compiled from different

studies suggest that patients with panic disorder show a dysregulation of the HPA [2], comprising a GABAergic dysfunction in the dorsomedial hypothalamus, which is activated by the OVLT when sensing increases in plasma lactate [127]. In depression, chronic inflammation can increase hypothalamic vasopressin production or glucocorticoid receptor resistance, both of which could act as a precedent for increased CRH levels, which intensifies the stress response system [68].

Role of the CVOs in chronic neurodegenerative diseases: *terra incognita*

In order to understand disease pathogenesis, it is vital to identify the key actors that participate in the initiation, progression and termination of the inflammatory reaction. Recent evidence suggests that the progression of Parkinson's disease can be due to an uncontrolled excessive inflammation that causes neuronal loss [50]. Cunningham et al. [26] demonstrated that systemic inflammation induced by injection of LPS in rodents with scrapie, an animal prion disease, acutely exacerbates cognitive and motor signs of disease and accelerates its progression. Alzheimer's disease (AD) and multiple sclerosis (MS) are two of the most prevalent human neurodegenerative disorders in which immunity and inflammation play a pivotal role in pathology [4, 138, 156, 157]. A putative link between the inflammatory processes, the sympathetic noradrenergic pathways and elevated plasma cortisol levels has been proposed in MS [159]. In none of these diseases, the role of the CVOs in their pathogenesis has been investigated.

Prion protein found in prion diseases is associated with chronic inflammation similar to that observed around amyloid plaques of AD [40]. Although disease-associated prion protein (PrP^d) deposition is found in the CVOs in preclinical sheep with scrapie [130; Fig. 5], it remains unknown whether neuroinflammation occurs before the deposition of extracellular protein, or as part of the repair process after neurodegeneration. In the following sections, we will discuss the possible role of the CVOs in prion diseases. For that purpose, we will focus mainly in some of the recent findings available from animal models.

Animal prion diseases: neuroinvasion can occur through the CVOs

Some viruses like reoviruses, herpesviruses and the rabies virus can be transported from axon terminals to the neuronal cell body, and vice versa, in a retrograde or anterograde manner, respectively. Recent investigations confirmed that rabies virus can also enter the CNS via blood, although it is unclear if they do so by crossing the BBB or through the

CVOs [112]. Similarly, prions can reach the CNS by neural routes [88]. In ovine prion diseases, neuroinvasion can occur by retrograde transport of infectivity along sympathetic and parasympathetic peripheral nerves [90, 131, 149]. However, a bulk of data generated by experimental studies on bovine spongiform encephalopathy (BSE) and scrapie in sheep and on chronic wasting disease in cervids have confirmed that blood is infectious; this notion has been further supported by transmission of the new variant of Creutzfeldt–Jakob disease between humans by blood transfusion (reviewed in [131]). Recent studies in sheep and goats infected with scrapie or BSE have shown that PrP^d accumulation in the CVOs is an early and consistent event that is not affected by the route of challenge or the agent strain [55, 131]. This has been interpreted to suggest that blood-borne prions can enter the CNS through the CVOs. PrP^d deposition in the CVOs has also been observed in mice infected with several murine strains and in cattle and deer infected with the BSE agent [131].

Role of the CVOs in the spread of prion infectivity to the brain parenchyma

In the case of prion diseases, the CVOs have been shown to accumulate PrP^d before adjacent structures of the brain parenchyma [55, 130]. It is likely that once infection is established in the CVOs, it could spread to interconnected neural structures. Thus, for example, PrP^d in the hypothalamic paraventricular nucleus and in the bed nucleus of the stria terminalis could result from spread from the SFO and from the OVLT (Fig. 5a–d). The involvement of the DMNV and of the AP is often simultaneous [55, 131], and it is shortly thereafter accompanied by accumulation of PrP^d in the STN (Fig. 5e). Interestingly, there is an absence of immunolabelling for some proteins that are specific for the BBB in the STN, supporting previous statements that this nucleus contains a proportion of fenestrated capillaries [58, 87]. All these issues make it difficult to determine if the mechanism of entry of infection at this level of the brain is through the vagus nerve or from the blood, or from both. Figure 6 highlights the initial brain structures that are stimulated by the neural or humoral pathways and their subsequent connections to other neuronal nuclei.

Could endocrine dysfunction in prion disorders be associated with pathology in the CVOs and related areas?

Several investigations point towards a dysfunction of the HPA and autonomic system in animal prion diseases. In 1964, Beck et al. [12] reported neural cell degeneration of the HPA axis in sheep with scrapie. Scrapie clinical signs include altered drinking and food intake behaviour caused by disturbances at the central level [9, 11, 12, 103–105].
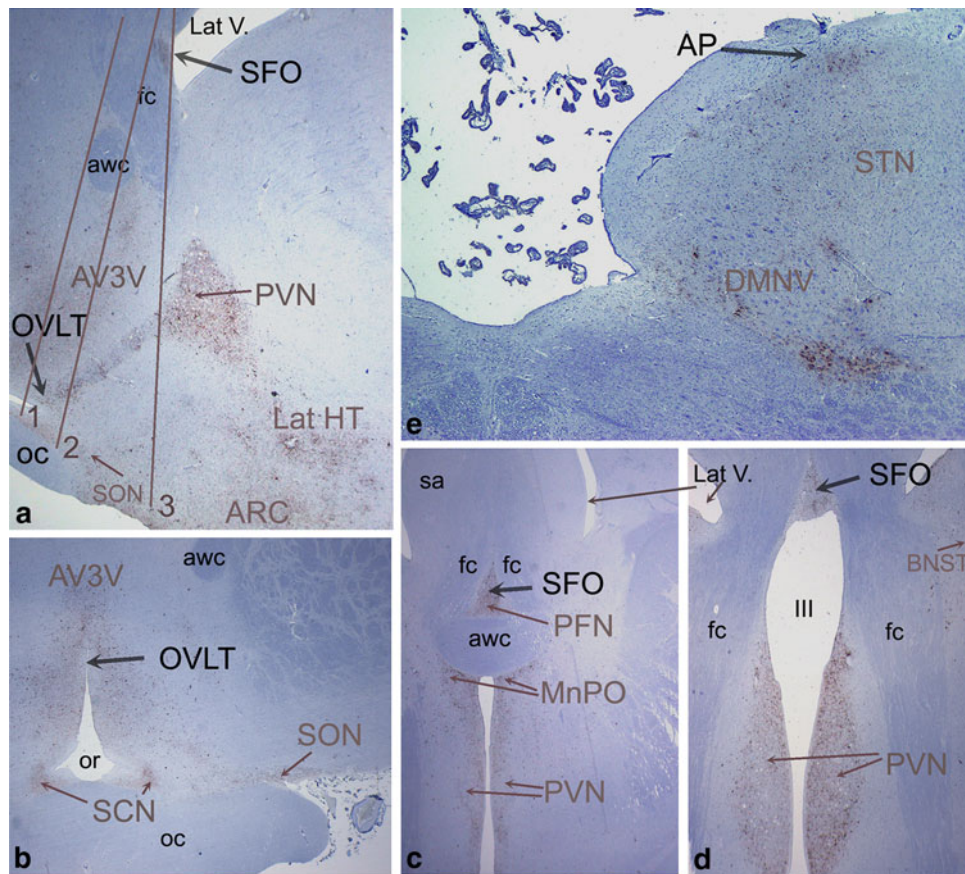
Fig. 5 Early deposition of PrP[d] in the sensory CVOs and related brain structures of scrapie-infected goats. **a** Sections 1, 2 and 3 show the location of the OVLT and SFO (*arrows*) at the level of the diencephalon in **b**, **c** and **d**, respectively. **e** The exact location of the AP at the level of the obex. PrP[d] accumulations are detected by immunohistochemistry in the CVOs and related structures rather than randomly. The exact location of the CVOs is indicated by *black arrows* whereas the location of related nuclei is denoted by *grey capital letters and arrows*. Neuroanatomical sites are in lowercase to assist with the section orientation. *STN* solitary tract nucleus, *DMNV* dorsal motor nucleus of the vagus nerve, *PVN* paraventricular nucleus, *Lat HT* lateral hypothalamic area, *AV3V* anterioventral part of the third ventricle, *SCN* suprachiasmatic nucleus, *SON* supraoptic nucleus, *ARC* arcuate nucleus, *PFN* perifornical nucleus, *MnPO* median preoptic area, *BNST* bed nucleus of stria terminalis, *lat V* lateral ventricle, *awc* anterior white commisure, *oc* optic chiasm, *fc* fornix columns; *or* optic recess, *sa* septal area. **a–d**: ×1; **e**: x4

Abnormal hormone plasma concentrations suggest alterations of the somatotropic (metabolic homeostasis and neuroprotection) and corticotropic (stress response) functions in sheep [51, 110, 119, 150] and rodents [158] infected with scrapie.

Endocrinopathies in patients with familial fatal insomnia or Creutzfeldt–Jakob disease include hypersecretion of cortisol, growth hormone and insulin growth factors, hyperinsulinaemia, altered glucose tolerance and/or insulin-resistant, adrenal-dependent obesity, loss of body weight, etc. [10, 85, 113]. While some research indicates that neurodegeneration and clinical signs are the result of the toxic effect of PrP[d], other investigations support the notion of an impaired physiological function of the normal cellular prion protein (PrP[c]). In that respect, experiments with PrP[c] knockout mice suggested that this protein might play an important role in the modulation of the corticosteroid-dependent negative feedback on the HPA axis [117].

Nevertheless, a full understanding of the nature of clinical disease in prion diseases is still lacking.

Abnormal heart rate variability has been described in sheep with scrapie as an early and clinically-silent abnormality [53], and possibly as a manifestation of the pathology targeting the DMNV. We hypothesize that sites like the CVOs, which accumulate PrP[d] at early stages, are more vulnerable to pathological changes, which would lead to early clinically-detectable abnormalities. On-going investigations in sheep with preclinical scrapie or BSE show PrP[d] deposition in brain areas that can be activated by both the neural and the humoral pathways (Figs. 5, 6), and this could lead to an early dysfunction of the HPA axis in these prion diseases. In sheep with clinical scrapie, there is a glial response characterized by diffuse astrocytosis and microglial activation restricted to the preoptic area of the hypothalamus. Brains of these sheep also show an increase in (i) vasopressin-containing fibres crossing the median
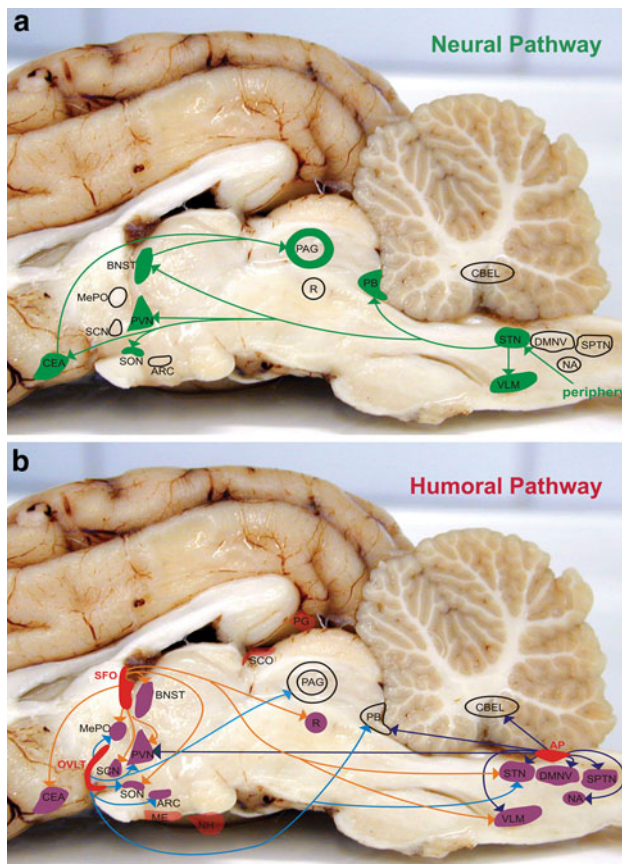
Fig. 6 Pathways of neuroinvasion in prion diseases. As illustrated in Dantzer et al. [30], there are two main pathways by which the immune system communicates with the brain in order to activate the hypothalamic-pituitary axis: a neural pathway (**a**) and a humoral pathway (**b**). In the neural pathway, peripheral visceral sensory afferent fibres of the vagus nerve stimulate the solitary tract nucleus, which have established connections with other nuclei highlighted in *green* (**a**). In the humoral pathway, circulating cytokines directly stimulate the CVOs (**b**) which have established connections with other nuclei (*arrows*) as reported in previous investigations [26, 76, 100]. Note that different *arrow colours* in **b** have been used to denote the CVO of origin. Investigations in sheep with preclinical scrapie or BSE indicate initial PrP^d deposition in the CVOs and in those neuronal nuclei that have been highlighted in *purple* (**b**). We believe that the fact that those nuclei are common to those involved in the stimulation of the HPA axis may suggest that abnormalities in this axis might be present early in prion diseases. The non-sensory CVOs like the median eminence (*ME*), the neurohypophysis (*NH*), the pineal gland (*PG*) and the subcommisural organ (*SCO*) are shown. *STN* solitary tract nucleus, *SPTN* spinal trigeminal nucleus, *DMNV* dorsal motor nucleus of the vagus nerve, *NA* nucleus ambiguous, *VLM* ventrolateral medulla, *PVN* paraventricular nucleus, *SCN* suprachiasmatic nucleus, *SON* supraoptic nucleus, *CEA* central amygadolid nucleus, *ARC* arcuate nucleus, *MePO* median preoptic nucleus, *BNST* bed nucleus of stria terminalis, *BNST* bed nucleus of the stria terminalis, *PBN* parabrachial nuclei, *PAG* periacqueductal grey matter, *R* raphe nuclei

eminence and terminating in the neurohypophysis, (ii) oxytocin-containing neurons within the suprachiasmatic and arcuate nuclei, and (iii) the number of neurons containing these two hormones in the supraoptic and paraventricular nuclei (S. Sisó and M. C. Garza, unpublished observations).

Opinion and perspectives

Because of its impermeable nature, an intact BBB protects the CNS from toxic agents and pathogens circulating in the blood. Disruption of the BBB is, therefore, a critical event in the initiation and progression of neurological disorders. There are, however, some tiny structures of the brain where the BBB is absent; those are the CVOs which, having fenestrated capillaries, enable their neurons to have a direct contact with blood-borne substances. In some infectious diseases, these organs can provide the route of entry for the pathogens into the brain activating a cytokine-transcription cascade producing prostaglandins (febrile response) that subsequently can disrupt the BBB resulting in widespread CNS pathology. At present, the relative contribution of the immunopathological mechanisms that take place in the CVOs and their cross-talking with the brain parenchyma possessing a BBB is not well defined.

The CVOs are pivotal for most autonomic and endocrine functions. Investigations of the CVO–HPA circuits could contribute to the detection of clinically-silent abnormalities at early stages of disease. Chronic CNS disorders with disruptions in the HPA axis include multiple sclerosis, depression, bipolar disorder, anorexia nervosa, schizophrenia, prion diseases and AD [139]. An improved understanding of the role of the CVOs in disease might allow the development of therapies aimed at blocking the entry of pathogens into the CNS or at modulating the acute immune response at a central level. Moreover, recent research [14] suggests that the CVOs provide a source of stem/progenitor cells that can proliferate and give rise to neurons or glial cells in the adult brain [82, 93]. For all these reasons, opportunities in future could emerge for targeting the CVOs not only to maintain health but also to aid recovery from injury or infection. Finally, CNS disorders are a major focus of the pharmaceutical industry, with drugs able to cross the BBB representing some of its most successful products. An additional way to side step the constraints of such a barrier are to design CNS drugs that may be taken-up by the blood vessels within the CVOs. These therapeutic strategies may benefit from increased knowledge on the properties of these organs.

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