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Review Article

Circumventricular Organs Part I

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Abstract

There are seven circumventricular organs in the rat brain, which have been given this classification because they are all located in the walls of the lateral, third, or fourth ventricles of the brain. The subfornical organ, the vascular organ of the lamina terminalis (OVLT), the pineal gland, the subcommissural organ, and the median eminence/neurohypophyseal complex are located in different places in the wall of the third ventricle. The area postrema is located in the wall of the fourth ventricle. The choroid plexus can be found in the lumen of the lateral, third, or fourth ventricle.

Keywords: rat; brain; circumventricular organs

Introduction

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General Characteristics

Although the structure is not uniform, several features distinguish the circumventricular organs from other brain regions. All are highly vascular structures and have an unusual vascular arrangement, with many capillary loops extending close to the ventricular surface. From a functional standpoint, perhaps the most interesting aspect of the vascular morphology is the presence of capillaries with fenestrated endothelial cells in all circumventricular organs except the subcommissural organ. This results in a disruption of the blood–brain barrier in all but one circumventricular organ, and, unlike the rest of the brain, there may be bidirectional movement of polar molecules between the hemal and neural milieu of the circumventricular organs. The ependymal cells that form the ventricular surfaces of the circumventricular organs also differ in appearance from the regularly contiguous cuboidal ependyma lining the rest of the ventricular surface. The ependymal cells of the circumventricular organs may be elongated or columnar and have an irregular appearance. They are either devoid of or have very few cilia on their luminal surfaces. This contrasts with the densely ciliated surfaces of normal ventricular ependyma. Another difference between the ependymal cells of the circumventricular organs and normal ependyma is the presence of tight junctions between adjacent cells. This restricts the passage of marker molecules such as horseradish peroxidase between the cerebrospinal fluid and the circumventricular organ interstitium and vice versa. Thus, the blood–brain barrier is thought to be shifted from the level of the capillary endothelium to the ependyma in the circumventricular organs [1,2,4].

The choroid plexus and subcommissural organ consist of one or more layers of modified ependymal cells and do not contain neural cell bodies. They were termed ependymal circumventricular organs by Kuhlenbeck, whereas the remaining circumventricular organs were termed paraependymal circumventricular organs because they have subependymal elements that are very different from those of the ependymal cells. Only the subfornical organ, the choroid organ of the lamina terminalis, and the area postrema contain neuronal perikarya. They have many features in common and have been classified as sensory circumventricular organs. These three circumventricular organs have extensive afferent and efferent neural connections and distinctive cytoarchitecture and cytochemistry. The remainder of this chapter reviews the structure, connectivity, and neurochemical characteristics of the three sensory circumventricular organs. Brief individual descriptions of the other circumventricular organs then follow [2, 4].

Subfornical Organ

The subfornical organ (also known as the intercolumnar tubercle in older literature) was originally discovered in the brain of the Australian bat Nictophylus timoriensis by Elliott Smith and first described in detail (in human brain) by Putnam. It is a prominent feature in Nissl-stained sections of rat brain. Situated in the anterior dorsal wall of the third ventricle, at the

confluence of the two interventricular foramina and the third ventricle, the rat subfornical organ lies ventral to the hippocampal commissure and caudoventral to the junction of the two fornical columns. Its dorsal end articulates with the tela choroidea, while the ventral stalk of the subfornical organ fuses with the median preoptic nucleus. Rostrally, the septal triangular nucleus borders the subfornical organ. The subfornical organ has been subdivided into several subregions by Sposito and Gross. Two major subregions can be clearly defined on the basis of neuronal connections, receptor density, vascularization, and function as indicated by expression of the immediate early gene c-fos. These are the inner "ventromedial core" and the peripheral "external shell". Like other circumventricular organs, the subfornical organ is highly vascularized. It contains an extensive network of capillaries taking the form of sinusoids and capillary loops. The perivascular space is extensive and labyrinthine, and both fenestrated and nonfenestrated capillary endothelia are observed. Intravascularly administered horseradish peroxidase penetrates the common intercellular space of the subfornical organ, suggesting that the entire organ is exposed to the hemal environment. The ventromedial nucleus of the subfornical organ is reported to have the highest capillary and neuronal density. Neurons are distributed throughout the subfornical organ and have been classified into two types in rats based on whether they have vacuoles. On the ventricular surface, ependymal cells are flattened. Cilia are absent from many ependymal cells in the central part of the subfornical organ, whereas isolated ependymal cells at the periphery exhibit tufts of cilia [5–8].

Afferent neural connections

Early studies in rats using Golgi lesions and techniques showed afferent neural input to the subfornical organ from the adjacent median preoptic nucleus and the triangular septal nucleus. A later study using anterogradely transported amino acids as tracers failed to confirm a projection from the septal triangular nucleus. Other studies using horseradish peroxidase or fast blue conjugates injected into the subfornical organ confirmed that the median preoptic nucleus provides the richest afferent input to the subfornical organ. Approximately 20% of neurons in the median preoptic nucleus with projections to the subfornical organ also show collateral branches projecting to the supraoptic nucleus. The other circumventricular organs in the lamina terminalis, the organ vascularis of the lamina terminalis, also have neurons projecting to the subfornical organ, with up to 30% showing collaterals connecting with the supraoptic nucleus. Additional sites of afferent input to the subfornical organ are the paraventricular hypothalamic nucleus; the medial preoptic, dorsal preoptic, and anterior hypothalamic areas; and the medial septum, but these are present at lower densities than in the lamina terminalis. Neurons in the zona incerta and nucleus reuniens of the thalamus also have projections to the subfornical organ, and together with the perifornical area of the anterior hypothalamus, these connections appear to terminate in the ventromedial nucleus of the subfornical organ and contain angiotensin II. Afferent neural connections to the subfornical organ from more caudal brain regions have also been identified. These projections originate from the locus coeruleus, dorsal and median raphe, lateral parabrachial nucleus, and nucleus of the solitary tract to the subfornical organ [5,7].

Efferent neural connections

Three major efferent projections from neurons of the subfornical organs were initially identified as the median preoptic nucleus, the organ vascularis of the lamina terminalis, and the supraoptic nucleus. These findings were subsequently confirmed and connections to the paraventricular hypothalamic nucleus (both parvocellular and magnocellular areas), anterior periventricular preoptic area, dorsal perifornical area, ventromedial area of the lateral preoptic area, and lateral hypothalamus were reported in two independent studies. Some subfornical neurons were found to have axons with branches projecting to both the supraoptic and hypothalamic paraventricular nuclei, although these are not common and most neurons in the subfornical organ project only to the side of the supraoptic nucleus ipsilateral to the side of the subfornical organ in which they are located. Other sets of terminal fields were identified when the anterogradely transported lectin Phaseolus vulgaris leucoagglutinin was injected into the subfornical organ. Neurons in the substantia innominata, the rostroventral parts of the bed nucleus of the stria terminalis, the rostral zona inserta, and the infralimbic area of the prefrontal cortex were additional targets of subfornical efferents identified with this tracer [5].

Studies with retrogradely transported tracers show that within the subfornical organ, neurons have a topographic distribution depending on the destination of their projections. Subfornical organ neurons projecting to the median preoptic nucleus, supraoptic and paraventricular hypothalamic nuclei, zona incerta, prefrontal cortex, and substantia innominata are distributed primarily in a ring-shaped arrangement at the periphery of the subfornical organ, with very few retrogradely filled neurons in its ventromedial nucleus. Two areas have been identified as the major targets of subfornical organ neurons that occupy the ventromedial nucleus of this circumventricular organ, and these were the false nucleus of the stria terminalis and the parvocellular divisions of the hypothalamic paraventricular nucleus. Recent tract-tracing studies in rats using neurotropic pseudorabies virus injected into peripheral sites such as the kidney, gut, salivary glands, heart, forelimb muscles, and sympathetic ganglia indicate that there are polysynaptic efferent neural pathways from the subfornical organ to these peripheral targets. These results indicate that the subfornical organ has the potential to influence sympathetic nerves supplying many peripheral organs and tissues [6,8].

The fibers exiting the subfornical organ into the above-mentioned terminal fields have two main trajectories. The first group of fibers emerges from the anterior part of the subfornical organ and travels ventrally rostrally to the anterior commissure and along the anterior margin of the median preoptic nucleus to enter this nucleus as well as the vascular organ of the lamina terminalis and the preoptic periventricular and supraoptic nuclei. Other efferent fibers proceed postcommissurally through the fornix and diverge with the stria terminalis to the medial and lateral hypothalamus, terminating in the supraoptic and paraventricular nuclei. Some postcommissural fibers turn rostrally and join precommissural fibers directed to the median preoptic and supraoptic nuclei [7].

Neuroendocrine aspects

Consistent with the idea that the subfornical organ is a site at which blood-borne humoral agents exert their central actions are the observations that this circumventricular organ contains receptor binding sites for a number of circulating hormones. These include amylin, angiotensin II (mainly the AT-1 receptor subtype), atrial natriuretic peptide, calcitonin, glucagon-like peptide-1 (GLP-1), relaxin, somatostatin, and vasopressin (V1 receptor). In addition, a calcium receptor that responds to small changes in extracellular Ca^{2+} concentrations and the lipopolysaccharide receptor CD14, which is involved in neuroimmune responses such as fever, have been identified in the subfornical organ. Nitric oxide synthase is abundant in neurons throughout the subdivisions of the subfornical organ [5,7].

The action of angiotensin II on the subfornical organ has been studied extensively, and it is clear that this octapeptide acts on receptors in the subfornical organ to stimulate neural pathways subserving drinking and pressor responses in rats. Studies of c-fos expression indicate that circulating angiotensin II stimulates Fos production in neurons throughout the

subfornical organ; however, neurons in the ventromedial nucleus are more sensitive to angiotensin II, and there appears to be a higher density of angiotensin II receptors in the ventromedial nucleus of the subfornical organ than at its periphery. This distribution contrasts with the peripheral distribution of osmosensitive neurons in the subfornical organ that project to the supraoptic nucleus. Of relevance to the action of angiotensin II on the subfornical organ are the observations of high concentrations of angiotensin-converting enzyme in this circumventricular organ, which may allow circulating angiotensin I to be converted to angiotensin II in the vicinity of subfornical neurons. Atrial natriuretic peptide antagonizes the dipsogenic action of angiotensin II, and the two peptides have overlapping distributions of their receptors in the subfornical organ and in the vascular organ of the lamina terminalis and area postrema, suggesting that the inhibitory effect of atrial natriuretic peptide may be on the primary angiotensin-sensitive neuron in the circumventricular organs [8].

The ovarian hormone relaxin can influence oxytocin secretion in pregnant rats via receptors in the subfornical organ. Circulating relaxin has been shown to increase c-fos expression in many neurons in the periphery of the subfornical organ that have efferent neural connections to the supraoptic and paraventricular nuclei, and electrophysiological data confirm that relaxin stimulates neuronal activity in this circumventricular organ in the rat. Systemically administered relaxin stimulates water drinking as well as vasopressin secretion in rats, and the dipsogenic effect is abolished by ablation of the subfornical organ. It is likely that the relaxin binding sites observed in the subfornical organ represent specific relaxin receptors that mediate water drinking induced by blood-borne relaxin [7,8].

In addition to angiotensin II receptors, neurons containing this peptide have been immunohistochemically identified in the rat subfornical organ. These neurons are distributed mainly in the periphery of the subfornical organ, and some have been shown to project to the median preoptic nucleus. Fibers containing angiotensin II, somatostatin, and luteinizing hormone-releasing hormone terminate in the subfornical organ. Some terminals are located near perivascular spaces and do not form synaptic contacts with other neurons, suggesting neurosecretion of peptides into the subfornical organ circulation [8].

Lamina Terminalis Vascular Organ

The lamina terminalis vascular organ forms the ventral portion of the midline anterior wall of the third ventricle. In the rat, it extends dorsally for approximately 1 mm from the optic chiasm and the roof of the optic recess, a small anteroventral extension of the third ventricle. It is bounded both rostrally and caudally by CSF spaces, namely the prechiasmatic cistern and the optic recess of the third ventricle, respectively. It is bounded by the diagonal band of Broca on its lateral margins, and the median preoptic nucleus lies immediately dorsal. The lamina terminalis vascular organ and the subfornical organ form the respective ventral and dorsal poles of a continuum of tissue that includes the intermediate median preoptic nucleus and is collectively referred to as the lamina terminalis. Embryologically, the subfornical organ and the vascular organ of the lamina terminalis originate from the same anterior pole of the neural tube and gradually separate during development by the ingrowth of fibers that eventually form the anterior commissure. It is therefore not surprising that, in addition to the absence of a blood–brain barrier, the two regions share common structure, neural connections, receptor types, neurochemical content, and function. The ependymal cells lining the vascular organ of the lamina terminalis have tight junctions (both zonnula occludens and zonula adsens) near their apical surfaces. As mentioned previously, this differs from the cuboidal ependymal cells lining the rest of the ventricular system, which have no junctions and therefore do not impede the flow of substances between the cerebrospinal fluid and the brain parenchyma [9,10].

The most striking morphological feature of the vascular organ of the lamina terminalis, like most circumventricular organs, is that it contains a rich vascular plexus with a specialized arrangement of blood vessels. It is this complex arrangement of blood vessels that has led to the division of the vascular organ of the lamina terminalis into an outer zone and an inner or parenchymatous zone. The small branches of the preoptic artery (which distribute from the anterior communicating artery) in the prechiasmatic cistern break up into a dense network of small vessels in the pia mater at the cisternal edge of the vascular organ, the lamina terminalis. Invaginations of the pia mater that enclose the capillary loops extend further into the organ in a Y-shape when viewed in horizontal section, and these two vascularized areas constitute the outer zone. The inner zone contains a complex neuropil with neurons, fibers, glia, capillary loops, and perivascular spaces extending to the ependyma. Many of the capillaries exhibit fenestrated endothelial cells. The tight junctions normally present between endothelial cells (the basis of the blood–brain barrier) are effectively displaced partly toward the ventricular surface and partly toward the capillaries in the tissue at the boundary between the lamina terminalis vascular organ and adjacent brain regions. The net effectiveness of the junctions between specialized ependymal cells (tanycytes) on the ventricular surface and between the convoluted basal processes extending to the margins of the lamina terminalis vascular organ is demonstrated by the spread of blood-borne substances such as horseradish peroxidase through certain parts of the lamina terminalis vascular organ but not into the surrounding neuropil or into the ventricular cerebrospinal fluid. Based on neuronal connections, neuronal phenotype, and c-fos expression, three functional subdivisions of the rat lamina terminalis vascular organ can be distinguished: the central capillary plexus, the dorsal cap region, and the lateral zone, which extends caudally around the central capillary plexus into the periventricular tissue [10].

The arterial supply of the fenestrated plexus of capillaries in the lamina terminalis is most commonly by one or two horizontally directed arterioles that branch from the anterior communicating artery and occasionally by an arteriole that branches from the anterior cerebral artery at the rostral margin of the organ. The venous drainage of the lamina terminalis is by four to eight veins that course in a caudal direction, with the dorsal veins draining into vessels directed toward the anterior commissure; others extend caudally and ventrally into the venous sinus. This venous drainage is continuous with the superficial network that ultimately drains the preoptic and retrochiasmatic areas. The location of the fenestrated capillary plexus in the lamina terminalis vascular organ and the presence of neurohormones and neurotransmitters in a secretory configuration around the perivascular spaces (see below) have led several investigators to propose a neuroendocrine role for the lamina terminalis vascular organ analogous to the median eminence portal system. The fact that the main venous drainage of the lamina terminalis vascular organ is into the medial preoptic area, where blood vessels are not fenestrated in the rat, is inconsistent with the concept of a portal system. In this regard, there is a poorly understood anastomosing vascular network that connects the lamina terminalis vascular organ to the subfornical organ, median preoptic nucleus, and vascular plexus. The function of this network as a conduit for neurohormones is unclear because the direction of blood flow is unknown. Between the centrally located vascular plexus and the outer margins of the vascular organ of the lamina terminalis is a complex inner zone consisting of a labyrinth of tanycyte processes, glial cells, and neural elements. The latter are characterized by small, "primitive" neuronal cell bodies and nerve terminals. Often these terminals contain neurosecretory granules and are aligned without synaptic

specializations along the basement membrane that forms the outer edge of the perivascular spaces surrounding the fenestrated blood vessels. The growing list of neuropeptide releasing factors and putative transmitters contained in these terminals includes luteinizing hormone-releasing hormone and somatostatin, vasopressin and oxytocin, and atrial natriuretic peptide. These terminals originate from cell bodies located primarily outside the vascular organ of the lamina terminalis [10,11].

Afferent nerve terminals of luteinizing hormone-releasing hormone arise from cell bodies in the adjacent preoptic area. Similarly, oxytocin fibers arise from cell bodies in areas surrounding the vascular organ of the lamina terminalis. Vasopressin fibers project to the vascular organ of the lamina terminalis from parent cell bodies located in the suprachiasmatic nucleus. Other areas known to project to the vascular organ of the lamina terminalis with an unspecified phenotype include other components of the lamina terminalis, the subfornical organ, and the median preoptic nucleus, as well as the medial and lateral preoptic areas, the anterior lateral and dorsomedial hypothalamus, the locus ceruleus, the central gray matter of the midbrain, and the paraventricular nucleus of the hypothalamus [11].

Efferent neural connections

Efferent pathways from the lamina terminalis vascular organ were studied by mapping the distribution of an anterogradely transported tracer after its microinjection into the rat lamina terminalis vascular organ. The main efferent pathway from the lamina terminalis vascular organ descends in the medial forebrain bundle, although smaller numbers of fibers pass through the periventricular area of the hypothalamus. There are reciprocal connections with the median preoptic nucleus and subfornical organ and the hypothalamic paraventricular nucleus. A few efferent fibers ascend dorsally to reach the parastriatal nucleus and the intermediate part of the lateral septal nucleus. There are also direct neural inputs to the supraoptic nucleus, arising mainly from a compact group of neurons in the dorsal lid of the lamina terminalis (as do neurons in the lamina terminalis that project to the magnocellular subdivisions of the paraventricular nucleus), and this has been confirmed by retrograde transport of tracer molecules injected into the supraoptic nucleus. These neurons are activated by systemic hypertension or dehydration and may represent a major group of physiological osmoreceptors regulating vasopressin secretion. Efferent connections with the parvocellular regions of the paraventricular nucleus are also present, and it is likely that most of these fibers originate in the lateral zone of the lamina terminalis. A strong projection from the lamina terminalis to the lateral hypothalamic area has been confirmed by retrograde tracing experiments. Other regions of the hypothalamus that receive secondary inputs from the lamina terminalis are the arcuate and periventricular nuclei. There are also connections with certain parts of the limbic system. These include efferent projections to the bed nucleus of the stria terminalis, which has been confirmed by retrogradely transported tracer, with this projection arising primarily from the more lateral parts of the lamina terminalis rather than the dorsal operculum. Tracer is retrogradely transported from the cingulate gyrus to the dorsal operculum of the lamina terminalis, confirming that there is a direct projection from the lamina terminalis to this area. More caudal regions of the brain that receive efferents from the lamina terminalis are the periaqueductal gray and the lateral parabrachial nucleus. As with the subfornical organ, pathway tracing studies with neurotropic pseudorabies virus indicate that there may be polysynaptic pathways from the OVLT to many peripheral organs and tissues. These data suggest that the OVLT connects to sympathetic nerves supplying the periphery, and this may be another way in which circulating factors can influence sympathetic vasomotor pathways. Such a circuit may provide an anatomical substrate for the effects of anteroventral third ventricular wall lesions in attenuating experimentally induced hypertension [12].

Neuroendocrine aspects

As mentioned above, the OVLT is the site of dense luteinizing hormone-releasing hormone containing fibers and terminals and may play a role in the regulation of estrous cycles. Nitric oxide synthase is also present in neurons and fibers in the OVLT, although its function in the OVLT has not yet been determined. Similar to the subfornical organ, the OVLT is rich in binding sites for several circulating peptides such as amylin, angiotensin II, calcitonin gene-related peptide; atrial natriuretic peptide, and relaxin, suggesting that neurons in the OVLT may be influenced by these circulating peptides [13].

With respect to vasopressin secretion, as well as mediation of osmotically stimulated vasopressin secretion, neurons in the dorsal capsule of the OVCT that project to the supraoptic and paraventricular nuclei may play a role in mediating the effects of the ovarian pregnancy hormone relaxin on vasopressin secretion. In contrast, neurons in the OVCT that exhibit angiotensin II receptors and respond with increased Fos production to intravenous angiotensin II are located primarily near the lateral borders of the organ and in its most caudal periventricular region, and it is possible that they play a role in the centrally mediated pressor effect and sodium appetite induced by circulating angiotensin II [14,15].

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