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Elizaveta I Bon *

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Opinion Article

Circumventricular Organs: Area Postrema, Median Eminence and Neurohypophysis, Subcommissural Organ, Pineal Gland and Choroid Plexus

Bon E.I *, Maksimovich N.Ye., Kokhan N.V.

Grodno State Medical University; Grodno State Medical University, 80 Gorky St,230009, Grodno, Belarus.

***Corresponding Author:** Elizaveta I Bon, Candidate of biological science, Assistant professor of pathophysiology department named D. A. Maslakov, Grodno State Medical University; Grodno State Medical University, 80 Gorky St,230009, Grodno, Belarus.

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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

Area Postrema

The area postrema, first described in detail (in the human brain) by Wilson, is located at the apex of the calamus scriptorius in the dorsomedial medulla. In most species it appears as bilateral rounded eminences on either side of the fourth ventricle at its entrance to the central canal. In the rat, most of these bilateral eminences have fused so that in coronal sections the area postrema appears as a hump or quadrant of tissue dorsal to the nucleus of the solitary tract. The ependymal cells of the area postrema are flattened, and small neurons surrounded by astrocytic cells and processes are found throughout this circumventricular organ. Axodendritic synapses are common, and axosomatic synapses are also present. Because of its rich vascularization, the area postrema has a spongy appearance. In describing this vascular network, Duvernoy and Koritke commented on groups of capillaries that were spiral in shape and gave rise to multiple subependymal capillary loops. Two types of capillaries were observed in the area postrema: large sinusoidal vessels and smaller capillaries. Fenestrated endothelial cells lined many of the capillaries in the area postrema, allowing them to bypass the blood–brain barrier. Perivascular spaces containing large nerve cells and processes containing both clear and dense vesicles were also observed [1,2,3].

Afferent Nerve Connections

Afferent nerve connections to the area postrema originate from only a few areas of the rat brain. The most abundant afferent input originates from the hypothalamic region in close proximity to the paraventricular and dorsomedial nuclei. This connection appears to be a continuous group of cells extending from the lateral parvocellular subnucleus of the paraventricular hypothalamic nucleus to the perifornical area and dorsomedial nucleus of the hypothalamus. In horizontal sections, this group of cells and dendrites appears as oval rings extending from a periventricular to a perifornical location at each end. A small number of cells in the lateral parabrachial nucleus have also been shown to project to the area postrema. There is also the possibility that the dorsal raphe and a few neurons in area A1 of the ventrolateral medulla and A2 neurons in the commissural and medial subnuclei of the nucleus of the solitary tract innervate the area postrema. However, Shapiro and Miselis considered it unlikely that neurons in these regions were retrogradely labeled by tracer injections into the area postrema, since the tracer would likely have extended beyond the edge of the area postrema [1,4].

In addition to this central input, the area postrema receives some fibers from the periphery. Vagal and glossopharyngeal fibers have been shown to terminate in the rat area postrema [1].

Efferent neural connections

Neurons of the area postrema connect primarily with neighboring areas of the nucleus of the solitary tract, especially with the dorsal part of its medial subnucleus. The densest terminal field is in the adrenergic group of C2 neurons, located midway between the solitary tract and the area postrema. A dense terminal field of fibers from the area postrema also surrounds the noradrenergic group of A2. There are few, if any,

connections in the dorsal motor nucleus of the vagus, but it has been suggested that some area postrema connections in the nucleus of the solitary tract terminate on the dendrites of vagal motor neurons with cell bodies in the vagal motor nucleus. Other medullary targets for area postrema efferents may include the ventrolateral medulla, the dorsal aspect of the spinal trigeminal tract and nuclei, and the paratrigeminal nucleus, although Cunningham and colleagues did not confirm these last two projections in a later study. They also questioned whether area postrema fibers terminated in the ventrolateral medulla. However, retrogradely transported tracers that were microinjected into the rostral ventrolateral medulla were transported back to noradrenergic cell bodies in the area postrema, suggesting a projection from the area postrema to the rostral ventrolateral medulla [4,5].

The most prominent area postrema efferent projection outside the medulla is to the dorsal pons, and the target of these fibers is the middle third of the lateral parabrachial nucleus. Two groups of neurons, one in the core and one in the lateral zone of the area postrema, project to specific subnuclei of the lateral parabrachial nucleus. In the case of the core, its projections are to the internal part of the external subnucleus and to the central and dorsal subnuclei, while the lateral zone projects to the external part of the external subnucleus. Cholecystokinin- and galanin-containing neurons are among the neurons in the area postrema that provide this neural input to the lateral parabrachial nucleus. The pericentral dorsal tegmental and dorsolateral tegmental nuclei may also receive input from the area postrema [1,4,5].

Neuroendocrine aspects

Fuchs and Ouman identified catecholamine- and serotonin-containing neurons in the rat area postrema. Subsequently, immunohistochemical studies of tyrosine hydroxylase and dopamine β-hydroxylase confirmed the presence of a group of norepinephrine-containing neurons in this circumventricular organ. Neurons containing GABA, substance P, enkephalin, neurotensin, and cholecystokinin, as well as serotonin-containing neurons, were also identified by immunohistochemistry. Some of the serotonin-containing neurons were shown to be associated with the lateral parabrachial nucleus. Unlike other sensory circumventricular organs, little or no nitric oxide synthase is observed in the area postrema. Because the area postrema neuropil is accessible to circulating humoral agents, the results of in vitro autoradiographic binding studies provide insight into possible hormonal influences that may be involved in area postrema functions. Binding sites for amylin, cholecystokinin, angiotensin, atrial natriuretic peptide, GLP-1, somatostatin, vasoactive intestinal polypeptide, neuropeptide Y, vasopressin, substance P, and insulin have been observed in the area postrema. With regard to cholecystokinin, systemic infusion of this hormone has been shown to induce Fos production in area postrema neurons, indicating that this is the receptor site for circulating cholecystokinin, although its major site of action appears to be on distal vagal afferents. Like other periventricular sensory organs, the area postrema exhibits the lipopolysaccharide receptor CD14 [6,7,8].

Neurons in the area postrema may be involved in baroreflex and cardiovascular regulation, with both angiotensin II and vasopressin acting on this periventricular organ to influence these functions. The area postrema probably plays a role in the control of food intake, body weight, and fluid homeostasis. It was previously suggested that the area postrema is a trigger zone for the gag reflex in cats. This idea has persisted since, with recent interest in the role of the area postrema in the action of antinausea drugs such as 5-HT3 antagonists. Although rats do not vomit, there is evidence that the area postrema in this species plays a role in the development of conditioned taste aversions associated with nausea [7,8].

Median Eminence and Neurohypophysis

The median eminence is a periventricular organ that is inappropriate to consider separately from the associated pituitary gland. The internal lamina of the median eminence is a continuation of the posterior pituitary gland or neurohypophysis, and the two share embryological and functional properties. The median eminence, or more accurately the ependyma that covers it, forms the floor of the third ventricle just caudal to the optic chiasm. Like other periventricular organs, the ependymal cells of the median eminence are irregularly shaped (usually flattened), lack cilia, and have intercellular junctions that restrict the passage of substances into and out of the cerebrospinal fluid. The median eminence is broadly divided into internal and external lamina. The internal zone is immediately adjacent to the ependyma and consists of subependymal glial cells, pituicytes, radially directed processes of tanycytes, and, most importantly, fibers of the supraopticoneurohypophyseal tract, which traverse the internal zone of the median eminence en route to the posterior pituitary gland. Unmyelinated fibers of this tract contain vasopressin and oxytocin and originate from magnocellular neurons in the paraventricular and supraoptic nuclei of the hypothalamus. In addition to en passage fibers, nerve endings are present in the internal zone, although the extent to which they form neurohemal or other contacts remains uncertain. These endings originate from catecholaminergic neurons in the brainstem or arcuate nucleus and form the reticuloinfundibular and tuberohypophyseal tracts. Peptidergic axons containing corticotropin-releasing factor or proopiomelanacortin pathway products also terminate in the inner zone. The outer zone contains a collection of glial cells, ependymal cells, and nerve terminals similar to those described for the inner zone, although the terminals are distinctly neurohemal. Importantly, there is a fenestrated vascular network called the primary portal plexus and, in close association with these vessels, an abundance of terminals containing neurohormones and releasing factors. The pars tuberalis forms the ventral surface of the outer zone of the median eminence, and the vessels of the portal system are found in this region [9,10].

The arterial supply of the neurohypophysis is entirely from the internal carotid artery. The anterior pituitary, on the other hand, does not receive a direct arterial supply but is perfused exclusively by long portal vessels arising from the primary portal plexus and, to a lesser extent, by short vessels arising from the neurohypophysis. This is a critical feature of the structure and function of the anterior pituitary, since it is through these portal vessels that pituitary hormones reach the anterior pituitary. This vascular anatomy, together with the absence of local nerve endings in the anterior pituitary, led early investigators to propose that the glandular pituitary was under the control of humoral factors released in the immediate vicinity of the portal vasculature. Since these early observations, considerable attention has been devoted to determining the nature and origin of the various pituitary factors released into the portal vessels and ultimately responsible for the release of anterior pituitary hormones, including thyroid-stimulating hormone, luteinizing hormone, prolactin, and adrenocorticotropic hormone [11].

Over the past 10–15 years, attempts to elucidate the various inputs to the median eminence and, in particular, the lamina externa have relied on the use of retrogradely transported tracers, immunocytochemistry, and sometimes a combination of both. Fibers in the

supraopticoneurohypophyseal tract of the zona internum clearly originate from the supraoptic nucleus and, to a lesser extent, from the paraventricular nucleus. Other afferent inputs, which are more likely to contain hypophysiotrophic factors, arise from the parvocellular paraventricular nucleus, periventricular hypothalamus, arcuate nucleus, vascular organ of the lamina terminalis, preoptic area, diagonal band of Broca, medial septum, and brainstem. For example, combinations of immunocytochemical and tracing studies have localized luteinizing hormone neurons projecting to the median eminence to the medial septum, diagonal band of Broca, preoptic area, perivascular organ of the lamina terminalis, and lateral hypothalamus. Although pooled experimental data of this type may not always be available, the anatomical overlap of the areas supplying afferents to the median eminence with the distribution of hypophyseal factors suggests possible origins for many of these factors. For example, thyrotropin-releasing factor is produced by cells in the diagonal band of Broca, medial septum, arcuate nucleus, and paraventricular nucleus. Dopamine, which has an inhibitory effect on prolactin release, is produced by cells in the arcuate nucleus, as are cells of origin of growth hormone-releasing hormone-containing fibers in the outer lamina. The distribution of somatostatin-containing cells is widespread, but those that project specifically to the median eminence are located in the periventricular hypothalamus. Corticotropin-releasing factor, the major agent responsible for adrenocorticotropic hormone release, is contained in the parvocellular neurons of the paraventricular nucleus. Vasopressin, also contained in the parvocellular neurons, has long been known to be present in nerve terminals in the outer lamina and to exert effects on adrenocorticotropic hormone release similar to those of corticotropin-releasing factor in various species, including the rat. The agents listed above are some of the major neurohormones contained in projections to the outer lamina of the median eminence; However, there are others, such as cholecystokinin, neurotensin, oxytocin, neuropeptide Y and dynorphin, that may have regulatory effects on the trajectories of the anterior pituitary and axons to the median eminence, but they are less studied [10,11,12].

Subcommissural Organ

The subcommissural organ, located in the posterior wall of the third ventricle, forms the dorsal roof of the entrance to the aqueduct of Sylvius and is located just ventral to the posterior commissure of the rat. This circumventricular organ is composed of sheets of elongated columnar ependymal cells that appear to have a secretory function. Secretion of glycoprotein into the cerebrospinal fluid by the cells of the subcommissural organ causes formation of the Reissner fiber. This acellular condensation of glycoprotein continues from the aqueduct of Sylvius throughout the central canal of the spinal cord. There are no neurons in the subcommissural organ, but there is neural innervation of specialized ependyma. Serotonergic fibers from the raphe provide part of this neural input. Like other circumventricular organs, the subcommissural organ exhibits a dense capillary network running beneath the ependymal cells, with some capillaries extending into the ependyma. Unlike other circumventricular organs, the capillaries in the subcommissural organ do not exhibit fenestrated endothelial cells; thus, the blood–brain barrier is preserved in this region [13,14].

The function of the subcommissural organ (and the Reissner fiber) remains unclear, although a number of earlier suggestions can be found in the literature regarding a role in fluid and electrolyte homeostasis or gonadotropin secretion. It has also been suggested that molecules secreted in the Reissner fiber may play a role in guiding brain and spinal cord development. Although the subcommissural organ is a distinctive feature of the rat brain and many other vertebrates, it appears to be absent from the human brain shortly after birth, although remnants of it may remain in the remnants of the mesocoelic recess [14,15].

Pineal Gland

This endocrine gland, found throughout the vertebrate phylum, has been the subject of interest for many centuries. In mammals, the pineal gland is a median cone-shaped structure located in the dorsocaudal roof of the third ventricle. It develops as a thickening of the ependyma around the pineal recess of the third ventricle and is attached by stalks to the habenular and posterior commissures. In the rat, most of the pineal cells have migrated dorsocaudally, so that the rat pineal gland is largely superficial, with a relatively long stalk that connects to the habenular and posterior commissures. This stalk contains nerve fibers, blood vessels, connective tissue, and parenchymatous cells. The rat pineal gland contains no neurons, but has many secretory cells known as pinealocytes. The other main cell type is a glial cell. Phylogenetically, pinealocytes evolved from photoreceptor neurons; however, in the rat, these cells have no direct sensitivity to light. Instead, a neural pathway from the eye via the sympathetic nervous system influences the secretion of melatonin and other indolamines from pinealocytes. This pathway originates in the retina, where neural signals are transmitted to the optic nerve via the retinohypothalamic tract, which branches directly from the optic chiasm to reach the suprachiasmatic nucleus. Here, synaptic connections are made with neurons projecting to the hypothalamic paraventricular nucleus. Another connection occurs here, and these neurons connect with sympathetic preganglionic neurons in the intermediolateral cell column of the spinal cord via a pathway that passes in the medial forebrain bundle and through the reticular formation. These sympathetic preganglionic neurons innervate the superior cervical ganglion, which in turn supplies the pineal gland and its melatonin-secreting cells via the nervi conari. Melatonin stimulation by pinealocytes depends on intact sympathetic innervation from the superior cervical ganglion, with dark-stimulating and light-inhibiting melatonin secretion. Studies in which neurotropic pseudorabies virus was injected into the rat pineal gland to trace the polysynaptic pathways to it from the hypothalamus support this pathway and show that neurons in the paraventricular nucleus that participate in this pathway are located in its dorsal, medial, and lateral parvocellular subdivisions. Retrograde tracing from the pineal gland of rats in which the superior cervical ganglion had been bilaterally destroyed revealed that neural inputs from the nucleus of the solitary tract and the salivatory nucleus via a synaptic connection in the sphenopalatine ganglion may provide parasympathetic input to the pineal gland [16,17].

Nerve fibers that probably originate from the habenular and posterior commissures were found to travel in and enter the pineal gland, and there is evidence suggesting direct central innervation from several brain regions. Such central innervation of the pineal gland could not be confirmed when care was taken to prevent any spillage of horseradish peroxidase injected into the pineal gland for retrograde tracing studies [17].

Choroid Plexus

This ion transport tissue has been grouped with the periventricular organs and is responsible for producing most of the cerebrospinal fluid formed in the central nervous system. The choroid plexus is found in the lateral,

third (dorsal recess), and fourth ventricles and is attached to the ventricular walls. It is a highly vascularized connective tissue that is enveloped in an extensively folded epithelial covering, giving it a "cauliflower" appearance when viewed with a scanning electron microscope. The epithelium is composed of cuboidal cells that sit on a basement membrane. These cells exhibit microvilli on the luminal surface and, together with the folding, provide a large surface area for the transfer of water and electrolytes between the hemal milieu of the choroidal interstitium and the ventricular lumen. The core of the choroid plexus contains numerous capillaries with fenestrated endothelial cells. The vessels are surrounded by perivascular spaces that are continuous with the interdigitating intercellular spaces of the choroidal epithelium. Although there are no barriers to the movement of tracer molecules such as horseradish peroxidase from the blood into the perivascular spaces of the choroid plexus, the zone occludens between adjacent epithelial cells provides the basis for a barrier between the blood and the cerebrospinal fluid. Sympathetic innervation from the superior cervical ganglion and vagal input provide neural regulation of the choroid plexus vasculature. The observation that the rat choroid plexus is rich in binding sites for many peptides, including insulin, vasopressin, and atrial natriuretic peptide, suggests that these peptides influence the function of this circumventricular organ, perhaps as local paracrine factors. It is also possible that they are taken up from the circulation by the choroid plexus epithelium and secreted into the cerebrospinal fluid. There is evidence that this occurs for thyroid hormones, leptin, and insulin-like growth factor I [18,19].

Like some other periventricular organs, the choroid plexus throughout the rat brain contains high concentrations of angiotensin-converting enzyme. This enzyme is found on the microvilli on the ventricular surface of epithelial cells, as well as on the membranes of the vascular endothelium. The functional implications of these histochemical findings remain to be determined.

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