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Report 2013: Tumors of the pineal region

Anatomical, molecular and pathological consideration of the circumventricular organs

Considérations anatomiques, moléculaires et pathologiques sur les organes circumventriculaires

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ABSTRACT

Background and purpose. – Circumventricular organs (CVOs) are a diverse group of specialised structures characterized by peculiar vascular and position around the third and fourth ventricles of the brain. In humans, these organs are present during the fetal period and some become vestigial after birth. Some, such as the pineal gland (PG), subcommissural organ (SCO) and *organum vasculosum* of the *lamina terminalis* (OVLT), which are located around the third ventricle, might be the site of origin of periventricular tumours. In contrast to humans, CVOs are present in the adult rat and can be dissected by laser capture microdissection (LCM).
Methods. – In this study, we used LCM and microarrays to analyse the transcriptomes of three CVOs, the SCO, the subfornical organ (SFO) and the PG and the third ventricle ependyma of the adult rat, in order to better characterise these organs at the molecular level. Furthermore, an immunohistochemical study of *Claudin-3* (CLDN3), a membrane protein involved in forming cellular tight junctions, was performed at the level of the SCO.
Results. – This study highlighted some potentially new or already described specific markers of these structures as *Erbb2* and *Col11a1* in ependyma, *Epcam* and CLDN3 in the SCO, *Ren1* and *Slc22a3* in the SFO and *Tph*, *Anat* and *Asmt* in the PG. Moreover, we found that CLDN3 expression was restricted to the apical pole of ependymocytes in the SCO.

Mots clés :
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RÉSUMÉ

Contexte et objectifs. – Les organes circumventriculaires (OCV) sont des régions spécialisées de l'épendyme situées autour du troisième et du quatrième ventricule avec une vascularisation particulière. Mieux connus chez l'animal, certains OCV sont atrophiés chez l'homme où ils sont présents le plus souvent sous forme vestigiale. Certains OCV comme la glande pinéale (GP), l'organe sous-commissural (OSC) et l'organe vasculaire de la lame terminale (OVLT), peuvent être à l'origine des tumeurs périventriculaires. Contrairement à l'homme, les OCV chez le rat sont présents à l'âge adulte et peuvent être étudiés par des techniques de microdissection laser (MDL).
Méthodes. – Dans cette étude, nous avons utilisé les techniques de MDL et de microarray pour étudier le transcriptome de trois OCV : OSC, l'organe subfornical (OSF) et GP ainsi que celui de l'épendyme du troisième ventricule chez le rat adulte. Nous avons également réalisé une étude immunohistochimique de la Claudine-3 (CLDN3), une protéine membranaire impliquée dans la formation des jonctions serrées au niveau de l'OSC.
Résultats. – Nous avons mis en évidence au niveau des OCV analysés des marqueurs moléculaires nouveaux ou déjà montrés dans ces structures comme *Erbb2* et *Col11a1* dans l'épendyme, *Epcam* et *CLDN3* dans l'OSC, *Ren1* et *Slc22a3* dans l'OSF et *Tph*, *Anat* et *Asmt* dans la GP. De plus, l'étude immunohistochimique a montré une expression de CLND3 uniquement au niveau du pôle apical des épendymocytes de l'OSC.

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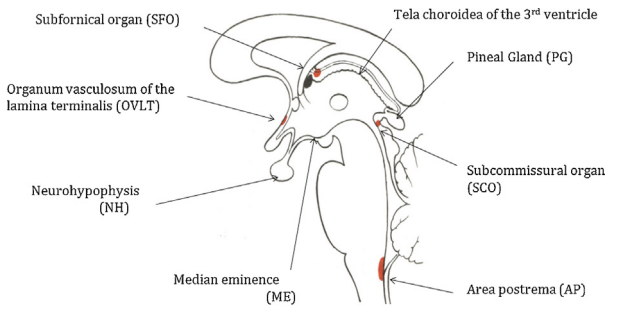

Fig. 1. Location of different Circumventricular organs (CVOs) around the third and fourth ventricle.
Coupe sagittale de cerveau humain montrant les organes circumventriculaires organes circumventriculaires (OCV).
Modified after [157].

Circumventricular organs (CVOs) are a diverse group of specialized structures characterized by peculiar vascular and position around the third and fourth ventricles of the brain. They are characterized by distinct morphological features and large perivascular spaces and almost all have fenestrated capillaries [1]. In humans, these organs are present during the fetal period and some become vestigial after birth [2]. Some, such as the pineal gland (PG), subcommissural organ (SCO) and *organum vasculosum* of the *lamina terminalis* (OVLT), which are located around the third ventricle, might be the site of origin of periventricular tumours [3]. We will describe these structures, their functions and realise a molecular study by microarray analysis of some CVOs in rat in order to highlight potential molecular structure signatures.

1. Definition and classification

The different CVOs are illustrated in Fig. 1 (modified from Kahle, 1979). Several classifications were described (summary in Table 1). Using morphological criteria, Kuhlenbeck [4] retains 2 types of CVOs: ependymal, with one or more modified ependymal layers, the SCO and choroid plexus; para-ependymal containing subependymal cellular elements others than ependymal cells: subfornical organ (SFO), PG, area postrema (AP), the neurohypophysis (NH) and the median eminence (ME). Other authors distinguish a group of neuronal or sensorial CVOs containing neurons: the SFO, the OVLT and the AP [5]. Moreover, the functional classification retains three types of CVOs [6]: sensorial CVOs, SFO, OVLT and AP, secretory CVOs, NH, ME and PG and OSC with an important neuroendocrine activity.

Several authors do not consider the choroid plexus (CP) as a CVO structure. In fact, the CP contains fenestrated capillaries but not neuronal tissue. Its major role is the production of cerebro-spinal fluid (CSF) regulated by different neuropeptides [7].

Table 1
Summary table of the circumventricular organ (CVO) classification.
Tableau récapitulatif des classifications des organes circumventriculaires (OCV).

CVO	SFO	OVLT	SCO	AP	PG	NH	ME	CP
Ependymal			+					+
Non-ependymal	+			+	+	+	+	
Sensorial	+	+		+				
Secretory					+	+	+	

SFO: subfornical organ; OVLT: *organum vasculosum* of the *lamina terminalis*; SCO: subcommissural organ; AP: *area postrema*; PG: pineal gland; NH: neurohypophysis; ME: median eminence; CP: choroid plexus.
SFO : organe subfornical ; OVLT : organe vasculaire de la lame terminale ; SCO : organe sous-commissural ; AP : area postrema ; PG : glande pinéale ; NH : neurohypophyse ; ME : éminence médiane ; CP : plexus choroïde.

2. Anatomy and function

2.1. Neurohypophysis (NH)

The NH corresponds to the posterior part of the hypophysis in all vertebrates. Nervous fibres originated from neurons of supraoptic nuclei (SON) and paraventricular nuclei (PVN) terminate at the level of the NH and they deliver the anti-diuretic hormone (vasopressin or ADH) and the oxytocin produced at the level of the hypothalamus. The oxytocin is implicated in the regulation of metabolic, sexual and maternal functions.

2.2. Median eminence (ME)

The ME is situated at the level of the floor of the third ventricle between the infundibulum and the mammillary bodies. One of its functions comes from the presence at the level of the arcuate nucleus (ARC), which is connected with the ME, of a great number of receptors for almost all metabolic active circulating hormones like insulin, glucocorticoid, leptin and ghrelin. Therefore, it was suggested that EM and the ARC should be considered as one functional unit [8].

2.3. Pineal gland (PG)

The pineal gland or epiphysis is a small organ (150 mg) in humans located at the back of the third ventricle. Until 1950s, the PG was considered as a vestigial organ. In 1958, Lerner et al. isolated a particular hormone, the N-acetyl-5-methoxytryptamine or melatonin, from bovine epiphysis and established its structure [9]. From the 1970s, the progresses in radioimmunoassay technique allowed to determine the level of melatonin in biological fluids. Moreover, the development of research in the field of biological rhythm revealed relations between the pineal gland and the biological clock. Some authors do not consider the PG as a CVO because of its neuroendocrine function.

In humans, the development of the PG begins as a bulge at the level of the roof of the diencephalon. At the seventh week of intrauterine life, the ependymal epithelium thickens then transforms in the epiphyseal pouch containing the epiphyseal ventricle. At the eighth week, the two epiphyseal lobes, anterior and posterior, are formed. At 20th week the fusion of two lobes occurs with the disappearance of the cavity witch becomes the pineal recess of the third ventricle.

Until the third month of intrauterine life, the pinealocyte cells present a big nucleus that becomes indented. The vascularisation develops from the third month with non-fenestrated capillaries (hemato-encephalic barrier). From the fifth month dense spots develop at the level of the nucleus dense core vesicles and synaptic ribbons together with the development of the gland innervation. Between the birth and 2 to 3 weeks of life, the pineal parenchyma shows a mosaic aspect with the juxtaposition of clear zones formed by clear cells surrounded by dark zones formed by dark cells. This aspect disappears after the 9th month after the development of fine cytoplasmic argyrophyl prolongations from pinealocytes.

In adult, PG represents an evagination of the diencephalon-ependymal roof between the habenular commissure at the superior level and the posterior commissure inferiorly where the gland is situated between the two superior colliculi. Anteriorly, the PG has relations with the third ventricle between the two thalami and at the beginning of the Sylvius aqueduct. The other relations are with the splenius of the *corpus callosum* and the pulvinar bodies laterally. The distance from different external points is equal [10].

The PG is composed of an external capsule, a glandular parenchyma, vessels and nerves. The capsule has a conjunctival origin with elastic and collagen fibres and contains mastocytes,

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