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The sensory circumventricular organs: Brain targets for circulating signals controlling ingestive behavior

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Abstract

Sensory circumventricular organs (CVOs) are specialized areas of the brain that lack a normal blood–brain barrier, and therefore are in constant contact with signaling molecules circulating in the bloodstream. Neurons of the CVOs are well endowed with a wide spectrum of receptors for hormones and other signaling molecules, and they have strong connections to hypothalamic and brainstem nuclei. Therefore, lying at the blood–brain interface, the sensory CVOs are in a unique position of being able to detect and integrate humoral and neural information and relay the resulting signals to autonomic control centers of the hypothalamus and medulla. This review focuses primarily on the roles played by the sensory CVOs in fluid balance and energy metabolism.

Keywords: Circumventricular organ; Subfornical organ; Area postrema; Organum vasculosum of the lamina terminalis

1. Introduction

The role of the autonomic nervous system is to respond to stress, regulate visceral function and maintain homeostasis. The hypothalamus and brainstem are recognized as areas of importance for the processing of sensory information and regulation of autonomic output. The purpose of this review is to highlight the roles played by a specialized set of structures, the sensory circumventricular organs (CVOs), in detecting changes in the composition of the peripheral circulation, integrating this information, and transmitting signals to the autonomic control centers of the hypothalamus and brainstem.

2. The BBB

2.1. Blood–brain barrier and the CVO's

The brain is in a privileged position in that it is essentially protected from unregulated exposure to constituents of the circulation. In contrast to the capillaries of peripheral tissue, the capillaries of most areas of the CNS contain no fenestrations and exhibit numerous tight junctions between endothelia. There are very few plasmalemmal vesicles and the vessels are surrounded by a continuum of astrocyte end feet, resulting in a highly restricted permeability of solute molecules into the CNS [1,2]. This restricted trans-capillary movement of blood-borne molecules into cerebral parenchyma gives rise to the idea of the blood–brain barrier (BBB). Molecules that cross the BBB under normal conditions are thought to do so by one of two mechanisms, diffusion or transport. Hydrophobic molecules (e.g. phenobarbitol, ethanol) are able to diffuse across the cell membranes of cerebral capillaries and into the CNS with the relative ease. Alternatively, hydrophilic molecules such as glucose, amino acids, and many other biological molecules must cross the blood–brain barrier by means of protein transporters. A few peptide hormones have been demonstrated to be transported across the blood–brain barrier via saturable (for example insulin [3] and leptin [4]), and non-saturable transport systems (for example growth hormone [5]). Therefore, the BBB acts to isolate the CNS from a variety of circulating molecules including many hormones, cytokines, and glucose. The BBB also protects the CNS from changes in osmolarity and electrolyte concentrations while ensuring that many neuropeptides, transmitters and growth factors do not diffuse out of the CNS into the circulation.

Thus, a problem arises. Changing levels of circulating hormones, electrolytes and metabolites, provide crucial

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feedback signals regarding the state of the "*milieu interieur*", however the BBB prevents this information from directly reaching autonomic control centers in the hypothalamus and medulla. While signals from afferent neural pathways such as the vagus do provide some sensory information regarding circulating signals (CCK levels for example), this information is limited, indicating that alternative centers for detecting circulating signals must be active. The sensory CVOs are specialized structures of the CNS that lack a BBB, and represent a window through which the autonomic nervous system gains direct information about the status of variables in the systemic circulation.

2.2. The CVOs

Circumventricular organs, so named because of their periventricular distribution within the CNS, are specialized midline structures found in the brains of all vertebrates. They are unique in that they are extensively vascularized and they possess highly fenestrated capillaries. The CVOs are thus not isolated by the BBB, but are uniquely situated to act as an interface between the brain and the periphery. In mammals, eight CVOs have been described; they are divided into two groups, the secretory, and the sensory. The secretory CVOs include the median eminence, the neurohypophysis, the intermediate lobe of the pituitary gland, and the pineal gland. The subcommisural organ is also considered to be secretory, however it is poorly understood, and appears to lack defining fenestrated capillaries of the other CVOs [6]. Some also consider the choroid plexuses to be circumventricular organs. The sensory CVOs include the subfornical organ (SFO), the organum vasculosum of the lamina terminalis (OVLT) and area postrema (AP). While some authors contend that the arcuate nucleus of the hypothalamus contains a "weak" BBB, to our knowledge there is no evidence suggesting that the physical properties of the capillaries therein are substantially different than those of other areas with an intact BBB. Additionally, it does not appear that substances can diffuse from the median eminence to the arcuate nucleus of the hypothalamus [7]. Of the eight CVOs, only the SFO, OVLT and AP contain neuronal cell-bodies; the other CVOs are comprised of terminals, axons, glia and epithelial cells. The anatomy and connectivity of the SFO, OVLT and AP are briefly reviewed below.

3. Anatomy/connectivity of the sensory circumventricular organs

3.1. Subfornical organ

The SFO protrudes into the third ventricle at the midline of the anterior wall. It is attached by a ventral stalk to the median preoptic nucleus (MnPO), and its dorsal crest attaches to tela choridea of the third ventricle. In coronal sections it noticeably protrudes into the third ventricle dorsal to the area of the lamina terminalis. Two functional zones of the SFO are generally recognized: the outer shell and ventromedial core [8]. The microcirculation within the SFO is complex: within parts of the shell, some capillaries possess a BBB, while within the core area many capillaries do not. Furthermore, in the core, capillary density may be of 4–5 fold higher than brain areas possessing a BBB, and capillaries here exhibit intermediate and large pericapillary spaces called Virchow–Robin spaces (areas where pools of interstitial fluid surround capillaries). The path of capillaries within SFO is tortuous, resulting in high blood volume and slow perfusion rates. Movement of solute out of capillaries in the areas lacking a BBB occurs at rates much higher than areas possessing a BBB, and the time that solutes "dwell" in SFO is quite protracted. This specialized vasculature probably serves to facilitate the sensory function of the subfornical organ [9–11].

The SFO sends direct and indirect projections to the paraventricular nucleus of the hypothalamus (PVN), supraoptic nucleus of the hypothalamus (SON) [12,13], median preoptic nucleus of the hypothalamus (MnPO) [13], the arcuate nucleus of the hypothalamus [14] and lateral hypothalamic nuclei [15]. Specific excitatory projections have been found to vasopressin- and oxytocin-secreting magnocellular neurons [16,17]. In addition, projections to parvocellular neurons of the PVN, which in turn project either to the median eminence [17], the medulla [18], or the spinal cord [19] have been observed. Afferent projections to the SFO emanate from the MnPO, the NTS, the lateral hypothalamus, midbrain raphe, the nucleus reunions of the thalamus [13,20,21].

3.2. Organum vasculosum of the lamina terminalis

The OVLT is a midline AV3V structure located ventral to the MnPO and dorsal to the optic chiasm. Two distinct regions within the OVLT have been described, the dorsal cap and the lateral region: the dorsal cap sends projections to the SON and magnocellular portion of the PVN [22–25]. Projections to CRH neurons have also been described [26]. Afferent projections to the OVLT arise from ventromedial nucleus, arcuate nucleus, anterior, posterior, and dorsal hypothalamus [23,27]. Much important information regarding OVLT function has come from lesion studies in which physiological changes associated with destruction of the OVLT or AV3V region have been attributed to OVLTs normal functions. The authors of the latter studies have been very careful not to specifically describe such AV3V lesions as OVLT lesions to ensure care in interpretation. They and others have highlighted that such AV3V lesions may also remove the contributions of both SFO and MnPO efferents.

3.3. Area postrema

The AP is located in the fourth ventricle, situated on the dorsal surface of the medulla immediately adjacent to the NTS. In rodents, the AP is a single midline structure; however in rabbits and primates, it is a bilateral structure. The AP is divided into three regions based on morphology of the neurons within and the projection of these neurons. These regions of AP include the mantle zone, the central zone and the ventral zone (which has been subdivided into the ventral-junctional zone and