Minireview

Morphological Aspects of the Median Eminence – Place of Accumulation and Secretion of Regulatory Neurohormones and Neuropeptides

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Abstract. The median eminence (ME) is a small brain area forming both the structural and functional bridge between the hypothalamus and the hypophysis It is supplied by a variety of neurohormones and neuropeptides which are delivered to the ME by different hypothalamic and extrahypothalamic pathways These biologically active substances may act in the ME locally influencing the activity of secretion of the neighbouring terminals or, after being released from the neuronal endings into the network of fenestrated capillaries and transported to the hypophysis, they may be involved in the regulation of secretion of adenohypophyseal hormones Recent demonstrations of extensive colocalizations of these biologically active substances in individual axonal endings in the ME with wide spectrum of biological actions further emphasizes the ME as an important place involved in the neuroendocrine regulatory processes

Key words: Median eminence — Neurohormones — Distribution — Transport — Secretion

Introduction

The median eminence (ME) represents one of the most important brain areas involved in the neuroendocrine regulatory processess, since it interconnects the two main neuroendocrine regulatory centers, the medial basal hypothalamus (MBH) and the hypophysis Thus, it serves as a substrate for the continual flow of informations from the brain to the pituitary, the principal regulator of the peripheral endocrine organs The ME is a place displaying many morphological peculiarities and place of accumulation and secretion of different neuropeptides and neurohor-

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mones into the hypophyseal portal circulation delivered from different brain areas The ME belongs to the circumventricular organs (organon vasculosum laminae terminalis OVLT subfornical organ SFO, subcommissural organ SFO, area postrema AP) (Fig 1) i e highly vascularized brain areas exposed to the cerebrospinal fluid Finally, the presence of the fenestrated capillaries makes the ME very susceptible to exchange of substances in both directions which classifies the ME as a blood brain barrier (BBB) free area

Morphological aspects of the ME

The ME forms a relatively small portion of the bottom of the brain extending from the beginning of the retrochiasmatic area to the stalk of the hypophysis It is predominantly composed of neuronal fibers and terminals occupying around 55 60% of the ME The second most widespread component of the ME are vessels (see below) which occupy roughly 22–30% of the ME The internal surface of the ME faces the cerebrospinal fluid (CSF), while the external surface the subarachnoidal space (Palkovits 1986)

The morphological variability of the structures forming the ME enables to distinguish 3 zones (layers) in the ME The CSF contacting ependymal zone is composed of specialized ependymal cells-tanycytes, which possess cilia-free surfaces and long basal processes assumed to participate in the transport of substances from the CSF to pericapillary space The rest of the ME is divided into the zona interna (ZI) and externa (ZE) The ZI mainly represents the route for axonal transport of substances to the posterior pituitary, and ZE is the site of secretion of substances into the portal circulation (Fig 1) Electron microscopic studies have explored more detailed stratification of the ME but their characterization exceeds the scope of this review

The ME is a highly vascularized area and in the rat, it is supplied by three hypophyseal arteries (in many mammals and in man by only two) arising from the circle of Willis or the internal carotid In the rat, these arteries supply the rostral part of the ME and the hypothalamic arcuate nucleus, the caudal ME and the stalk, and the posterior pituitary and retroinfundibular area This fenestrated network of vessels forms in the EZ the primary capillary plexus from which "capillary loops' emerge towards the midline of the ME up to the subependymal layer forming subependymal plexus The blood from this capillary network is collected by several long portal veins and transported to the adenohypophysis (Page et al 1978)

One of the most important properties of the ME is the well developed pericapillary space distributed between the two neuropil and capillary basement membranes (Fig 1), forming labyrint-like cavities around the vessels This is the most important portion of the ZE, i e the meeting point of the transport routes by blood vessels, basal spinal fluid space, and nerve terminals Different substances enter the

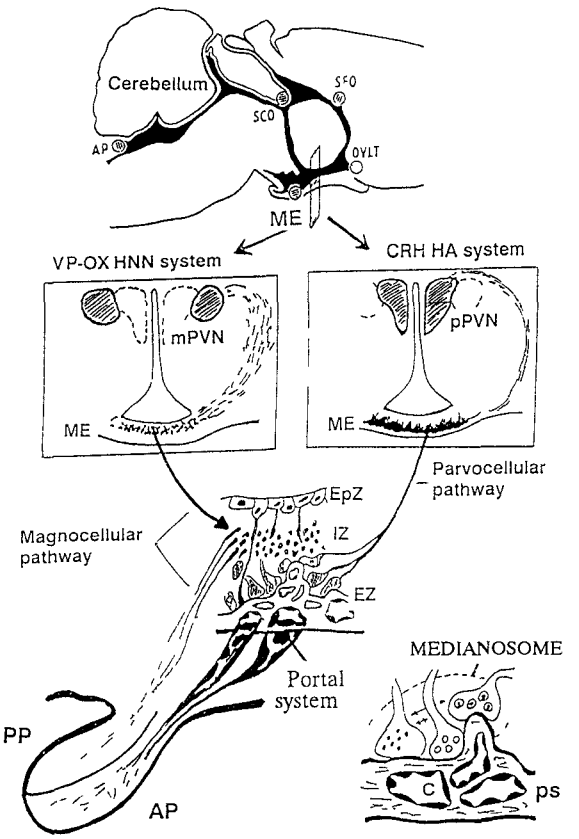

Figure 1. Schematic drawing of the magnocellular vasopressinergic and oxytocinergic (VP-OX HNN) and parvocellular corticotropin-releasing hormone (CRH HA) systems projecting to the hypophysis by different routes The VP-OX HNN system arising from the magnocellular neurons of the hypothalamic paraventricular nucleus (mPVN) sends direct axonal projections to the posterior pituitary (PP) by crossing the internal zone (IZ) of the ME localized immediately below the ependymal zone (EpZ) In contrast, axonal projections of the CRH HA system arising from the parvocellular neurons of the hypothalamic paraventricular nucleus (pPVN) terminate in the external zone (EZ) of the ME close to the capillary network from where the released CRH neurohormones are delivered to the anterior pituitary (AP) by humoral, i e portal blood system route Right lower corner Schematic drawing of a medianosome, an integrative functional unit, formed by 3 different nerve endings attached to the basement membrane of the pericapillary space (ps) of the EZ of the ME, where several capillaries are seen (C) Top picture shows the distribution of the different circumventricular organs (for abbrevations see the text) including the ME along the brain ventricular system (black)

pericapillary space by not yet exactly explained mechanism, but the majority probably by exocytosis, and cross to the fenestrated capillaries towards the portal blood

Increased levels of the substances in the portal blood measured under different experimental conditions clearly indicate that the downflow transport of substances i.e. transport from the brain and the ME, is physiologically the most important event in the neuroendocrine regulatory processes towards the hypophysis.

Distribution of neurohormones and neuropeptides in the ME

The ME has been the place of interest of neuromorphologists as well neurophysiologists for many years. All the biologically active substances described in the brain have been shown to be also present in this small structure even in higher concentrations (Palkovits 1986). The main source of these substances is the mediobasal hypothalamus (Fig. 2). Several morphologically and functionally well defined hypothalamo-ME pathways have been described so far. The first described connection is the "hypothalamo-neurohypophyseal neurosecretory tract" (Figs. 1, 2) arising from the hypothalamic paraventricular, supraoptic, and accessory magnocellular nuclei (Zimmerman et al. 1984). Massive axons of this pathway reach the ME via the retrochiasmatic area. Although the majority of these fibers carries vasopressin and oxytocin via the internal zone of the ME to the posterior pituitary many other neuropeptides such as corticotropin-releasing hormone (CRH), enkephalins, dynorphins, cholecystokinin and angiotensin II have also been demonstrated among these fibers. However, the peripheral physiological importance has only been clearly es-

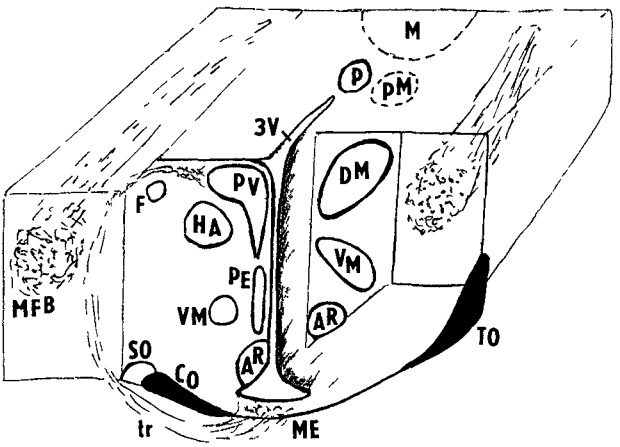

Figure 2. Anatomical organization of the rat mediobasal hypothalamus. AR – arcuate nucleus, PE – periventricular n., PV – paraventricular n., VM – ventromedial n., DM – dorsomedial n., HA – anterior hypothalamic n., SO – supraoptic n., P – posterior hypothalamic n., PM – premamillary nuclei, M – mamillary nuclei, ME – median eminence, F – fornix, MFB – medial forebrain bundle, CO – optic chiasm, TO – optic tract, 3V – third ventricle, tr – hypothalamo-neurohypophyseal tract.

tablished in some of these hormones including AVP and OXY The second well described hypothalamic-ME system is the parvocellular "hypothalamo-adenohypophyseal pathway" which was however fully described and understood after the CRH neuropeptide the principal regulator of the anterior pituitary corticotrops (Plotsky 1991) was isolated (Vale et al 1981) This pathway starts in the parvicellular CRH containing neurons of the PVN (Merchenthaler et al 1982) from where the fibers turn around the fornix and enter the ME through the retiochiasmatic area, to terminate in the palisade zone of the ME (Fig 1) However, recently it has been demonstrated that certain populations of CRH neurons coexpress AVP which is also present in around 50% of CRH terminals in the EZ of the ME (Whitnall et al 1987) The AVP has been shown to also be involved in the regulation of pituitary adrenocorticotrops (de Goeij et al 1992) Thyrotropin-releasing hormone (TRH), which was chemically characterized in 1969, also heavily contributes to the hypothalamic-tuberoinfundibular system arising from the PVN neurons characteristically accumulated almost immediately beneath the ependyma of the 3rd ventricle (Lechan and Jackson 1982) Lesion of the PVN causes a prompt reduction in plasma thyroid stimulating hormone levels (Arizava and Greer 1981) The hypothalamic arcuate nucleus (ARC) is another hypothalamic structure having a close relationship to the ME, even from two points of view First it is the only structure directly receiving blood supply from the anterior hypophyseal artery, and secondly the ARC sends two kinds of projections to the ME known as 1) the tuberoinfundibular dopaminergic pathway terminating near the perivascular space of the primary capillary plexus, and 2) the tuberohypophyseal dopaminergic pathway terminating in the neurointermadiate lobe of the hypophysis (Leranth et al 1996) However, some of the cells of the tuberoinfundibular pathway are located in the ventral premamillary, the ventromedial, the dorsomedial, the periventricular, the posterior hypothalamic nuclei, and this pathway therefore can carry many other substances including ACTH and β-endorphin By both the immunohistochemical and radioimmunoassay methods it has been demonstrated that the ARC is the main source of neurotensin (NT) of the EZ of the ME (Kiss et al 1987) The ARC is also the source of the growth hormone-releasing factor (GRF) containing terminals distributed around the capillaries of the portal vessels (Ibata et al 1986) In contrast, somatostatinergic innervation of the ME arises from the periventricular nucleus of the anterior hypothalamic area (Epelbaum et al 1981) which does not reach the ME by direct pathway, but before re-entering the mediobasal hypothalamus, it forms loops across the medial forebrain bundle In the case of galanin both the arcuate (by 30%) and PVN (by 70%) nuclei supply the ME by nerve terminals (Palkovits et al 1987) While many of the neuropeptides reach the ME via quite well known pathways (4 pathways have been described in the case of the LH-RH, Hoffman and Gibbs 1982), some other substances (adrenaline, histamine, serotonin) reach the ME by not yet exactly described hypothalamic or

extrahypothalamic routes (Palkovits 1986) More extensive information have been collected about the distribution of the substances in the ME regarding the stratification throughout the whole ME or within a single zone Immunohistochemical techniques have shown that the individual neurohormones and neuropeptides in the ME exhibit some characteristic features in their distribution in the ME i e LH-RH (Hoffman and Gibbs 1982), and galanin (Dutriez et al 1997) show massive lateral accumulation in the EZ ME while CRH is rather central, and AVP is very low in the EZ ME (Kiss et al 1989)

Secretion of neurohormones and neuropeptides in the ME

Today there is no doubt that the biologically active substances released from the ME reflect physiological processes of activation of neurons in the brain and stimulation or inhibition of target cells in the hypophysis In spite of the fact that axonal projections in the internal zone do not really release any product at the level of the ME because their contents are delivered to the posterior pituitary (Fig 1) they may exhibit density variations also at the ME level For example, osmotic stress almost completely depletes vasopressin immunoreactivity from the internal zone of the ME due to increased AVP secretion into the general circulation from the posterior pituitary (Mink et al 1986) However, more complicated relationships may exist with respect to the mechanism of secretion in the ME external zone No real synaptic apparatus is developed in the terminals of axonal profiles present in the ME and exocytosis serves as the most probable mechanism of substance release Based on the present knowledge it is really impossible to state if the organization of the terminals in the ME does or does not follow some developmental rules Globally some of the terminals seem to have direct contact with the basal membrane of the pericapillary space, while some others do not establish such contacts The latter may exert their effects within the ME by stimulating or inhibiting the release or uptake of other substances With regard to this situation, a hypothesis has been promoted that the ME external zone does not consist of diffusely spread out nerve terminals but forms well-defined aggregates of nerve terminals constituting so called median osomes instead The median osome (Fig 1) is thought to be an integrative unit in which nerve terminals using different neurotransmitters communicate with each other in well defined circuits (Agnati et al 1984) Since a functional relationship has been shown between small groups of terminals influencing or modulating each others secretion (Fuxe et al 1986), it cannot be ruled out that some functional relationship is being established during the maturation of the whole system During the recent few years, many neuropeptides have been shown to be colocalized in terminals of the ME external zone, which opens much more variation possibilities from cell to cell communication between hypothalamic neurons and adenohypophyseal cells CRH and AVP colocalization has been most

exactly described not only as a morphological phenomenon (Whitnall et al 1987) but also as a functional unit Although the functional activity of the colocalized AVP is closely related to the actions of the CRH by increasing its stimulatory effect on the ACTH release (Škultétyová et al 1997), it was demonstrated that vasopressin in subpopulations of CRH/AVP neurons can be separately released from the ME by stimulating the alpha-adrenergic receptors of CRH neurons in the PVN (Whitnall et al 1993) This is still a new view of the separate regulation of secretion of colocalized substances, and has to be proved also with respect to other substances Much effort has also been spent to find the way how to follow the amounts of substances in the ME released in response to different stimuli Along with the radioimmunological methods (RIA) used to measure susbstances in the isolated ME tissue an elegant modification of the colchicine technique utilizing blockade of the neural transport of substances from the cell bodies to ME by i c v application of colchicine was published by Berkenbosch and Tilders (1988) This technique enables to follow visually or by RIA measureaments the release of the actual amounts of immunostained neuropeptide in the ME under different experimental conditions However, there exist many more techniques including microdialysis push-pull perfusion, punching dissections, transections, lesions, superfusions, pharmacological treatments, enabling to follow the dynamics of neuropeptides in the ME under normal and experimental conditions, and to look for the physiological significance of the substances released Although neither of them may itself completely explore all the processess occurring in the ME each of them may add a piece of information to set up the final picture of the ME

Conclusion

This brief survey indicates that the ME is a very complicated brain area from both the structural and physiological points of view playing a crucial role in the regulation of the secretion of hypophyseal hormones Although a lot of information have already been collected about the structural and functional properties of the ME utilizing many different techniques, it is still a structure which might display many interesting events

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