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Neuro-immune interactions in the dove brain

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ABSTRACT

Mast cells (MC) are of hematopoetic origin. Connective tissue type MCs are able to function in IgE dependent and independent fashion, change their phenotype according to the tissue environment. They are able to enter the brain under normal physiological conditions, and move into this compact tissue made of neurons. In doves MCs are found only in the medial habenula (MH) and their number is changing according to the amount of sex steroids in the body.

MCs are able to synthesize and store a great variety of biologically active compounds, like transmitters, neuromodulators and hormones. They are able to secrete GnRH. With the aid of electron microscopy we were able to describe MC–neuron interactions between GnRH-positive MCs and neurons. Piecemeal degranulation (secretory vesicles budding off swollen and active granules) seems to be a very efficient type of communication between MCs and surrounding neurons. Different types of granular and vesicular transports are seen between GnRH-immunoreactive MCs and neurons in the MH of doves. Sometimes whole granules are visible in the neuronal cytoplasm, in other cases exocytotic vesicles empty materials of MC origin. Thus MCs might modulate neuronal functions. Double staining experiments with IP3-receptor (IP3R), Ryanodine-receptor (RyR) and serotonin antibodies showed active MC population in the habenula. Light IP3R-labeling was present in 64–97% of the cells, few granules were labeled in 7–10% of MCs, while strong immunoreactivity was visible in 1–2% of TB stained cells. No immunoreactivity was visible in 28–73% of MCs. According to cell counts, light RyR-positivity appeared in 27–52%, few granules were immunoreactive in 4–19%, while strong immunopositivity was found only in one animal. In this case 22% of MCs were strongly RyR-positive. No staining was registered in 44–73% of MCs. Double staining with 5HT and these receptor markers proved that indeed only a part of MCs is actively secreting. Resting cells with only 5HT-immunopositivity are often visible.

The activational state of MCs is changing at higher estrogen/testosterone level, thus with the secretion of neuromodulators they might alter sexual and parental behavior of the animals.

1. Introduction

Mast cells (MC) are of hematopoetic origin. Connective tissue type MCs are found in many tissues including the brain of birds and mammals under normal physiological conditions also. They enter the brain as mature cells [47,36], covering their c-kit receptors [31]. In birds MCs are found in the habenular region (medial habenula, MH) of the thalamus. Among mammals MCs in higher number in the habenular nuclei are found only in hedgehogs [15]. MCs have very distinctive morphology among other cell types in the brain. They have a round, mostly centrally located nucleus and many granules in their cytoplasm. These granules contain many MC products, presynthesized and stored; the skeleton of these granules is built on proteoglycanes. Proteoglycanes stain with acidic toluidine blue (TB, Fig. 2). The color of the granules after TB labeling changes according to the activational state of MCs, and consequently, so does the amount of proteoglycans in them. These cells, using the products stored in the granules, are able to open the blood–brain barrier, loosen the extracellular matrix around endothelial and glial cells in the neuropil of the brain [29,36]. With the aid of their fine filopodia they move deeper into the brain tissue. Two types of product secretion appear upon MC stimulation. Through IgE dependent activation MCs secrete with anaphylactic reactions (compound exocytosis), while in an IgE independent fashion with a more delicate exocytosis [12].

MCs display a secretory cycle (Fig. 1, [43]). Cells are found in different conditions, from resting state (Fig. 1I) to the fully degranulated phase (Fig. 1III). Piecemeal degranulation seems to be a general function of secretory cells [5] and neurons also [4]. This form of regulated exocytosis appears in active cells. Dense granules become swollen, particulate and vesicles bud off from granule membranes, moving towards the cell membrane or filopodia of MCs (Fig. 1V; [6]). After a very active state, when granule products are almost fully secreted, MCs are in the resynthesizing phase (Fig. 1IV). In this stage of the cycle only few dense granules are

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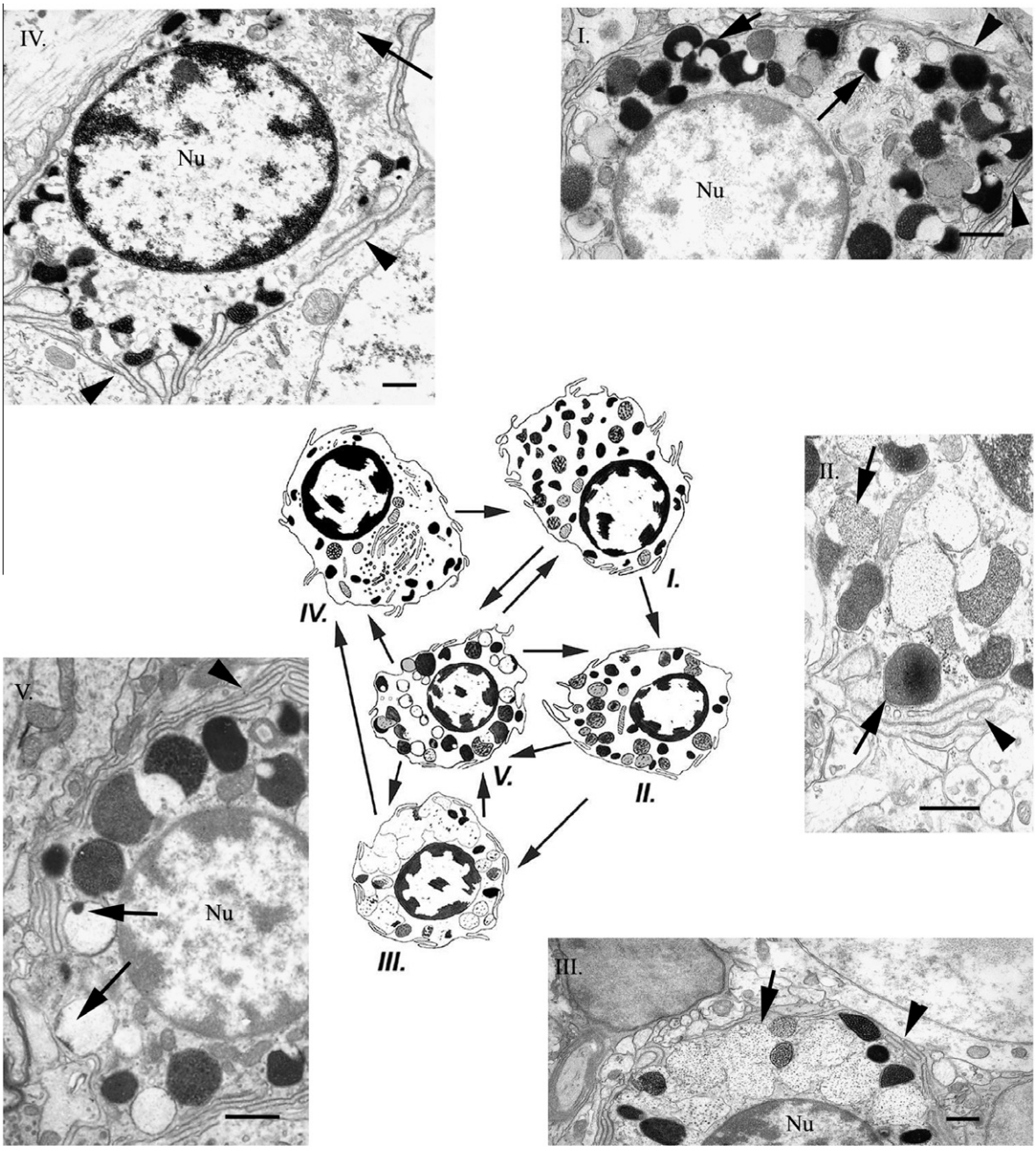

Fig. 1. Scheme of the secretory cycle of a MC. In a resting MC (stage I) mostly dense granules are found in the cytoplasm. Many of these granules have a semilunar appearance. The big, round nucleus is found in the center, or in slightly excentric position. Fine filopodia around the cell are often visible, just like cell organelles in the cytoplasm (mitochondria and ER). In stage II cells are degranulating. Most of the granules are swollen, less dense, more particulate and rounded. Some of the granules fuse, creating a fusion chamber. This way exocytosis is faster and the cell membrane opens only at one point upon exocytosis. In the fully degranulated state (stage III) most of the granules are swollen, very particulate. Many granules create a huge fusion chamber. From the fully degranulated state MCs enter the resynthesizing stage (stage IV). In this phase the nucleus is close to the cell membrane, only few granules are visible in the cytoplasm. These are mostly dense, and are at the cell membrane. A huge endoplasmic reticulum and Golgi fills the cytoplasm. In the state of piecemeal degranulation (stage V) MCs show a big range of granule size and structure. Many of the granules appear empty, but some dense material is recognizable at the granule membranes. Vesicles budding off the granules are abundant in the cytoplasm, or at the cell membrane. Scale bar: 1 μm on each electron micrograph.

visible close to the cell membrane. Very abundant endoplasmic reticulum (ER) and Golgi apparatus shows intensive compound synthesis.

Birds kept in visual isolation from conspecifics have few MCs in the MH, while after pairing them in one cage courting starts immediately. After 2 h of courtship the number of MCs increases dramatically (about tenfold the original number [33]. This number remains stable until the eggs hatch. Courtship is the beginning of a cascade of events leading to reproductive readiness, mating, and parental behavior in this species [32]. This reproductive behavior leads to the increase of the level of sexual steroids [7]. MCs in the brain were shown to store and secrete GnRH, while from mucosal MCs in the periphery this hormone is absent [46,34,37]. In rats MC number was found to be higher in females, than in males [10]. The peak MC numbers were observed at the lateral habenular nucleus and declined towards the anterior and posterior borders of the thalamus. Generally they do not accumulate in the MH. In cycling adult females MC number, degranulation state and the staining characteristics of the cells changed in the ovaries, uterus and brains, according to the estrogen level [1]. MCs were