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Review

Functional implications of the Golgi and microtubular network in gonadotropes

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ABSTRACT

In contrast to the widely accepted images of the Golgi apparatus as a cup-like shape, the Golgi in pituitary gonadotropes is organized as a spherical shape in which the outer and inner faces are cis- and trans-Golgi elements, respectively. At the center of the spherical Golgi, a pair of centrioles is situated as a microtubule-organizing center from which radiating microtubules isotropically extend toward the cell periphery. This review focuses on the significance of the characteristic organization of the Golgi and microtubule network in gonadotropes, considering the roles of microtubule-dependent membrane transport in the formation and maintenance of the Golgi structure. Because the highly symmetrical organization of the Golgi is possibly perturbed in response to experimental treatments of gonadotropes, monitoring of the Golgi structure in gonadotropes under various experimental conditions will be a novel in vivo approach to elucidate the biogenesis of the Golgi apparatus.

Contents

1. Introduction . . . 88
2. Structural characteristics of the Golgi apparatus and microtubule network within rat pituitary gonadotropes . . . 89
3. Influences of extrinsic stimuli to the GnRH receptor on the organization of the Golgi in pituitary gonadotropes . . . 92
4. Diversity of the global organization of the Golgi and microtubule network . . . 93
   4.1. Diversity of the Golgi organization of pituitary endocrine cells . . . 93
   4.2. Comparison of exocrine acinar cells and the acinus . . . 93
5. Concluding remarks and perspectives . . . 94
   Appendix A. Supplementary material . . . 95
   References . . . 95

1. Introduction

The pituitary gonadotrope is a representative endocrine cell that synthesizes and releases two distinct peptide hormones, luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Besides these two gonadotropins, gonadotropes secrete a large amount of soluble proteins such as chromogranins and secretogranins (Chanat et al., 1988; Cozzi and Zanini, 1986). Morphologically, gonadotropes contain two different types of secretory granules, small granules containing secretogranin II and large granules containing chromogranin A (Hosaka et al., 2002; Watanabe et al., 1998, 1993, 1991). To generate a large amount of secretory granules containing hormones and related proteins, the endomembranous organelles that constitute the exo- and endo-cytic pathways are well developed/organized in gonadotropes.

Among the endomembranous organelles, the Golgi apparatus is situated at the center of the secretory pathway and functions as an intersection of intracellular vesicular transport. The Golgi apparatus was first identified as a reticular structure in neurons using a silver impregnation method to stain the cells (Golgi, 1898a,b). Later, the intracellular structure stained by the silver impregnation method was ubiquitously observed in various cells at light microscopic levels, although the debate on the reality of the organelle

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lasted for a long time (for reviews on the issue including related references, see Beams and Kessel, 1968; Farquhar and Palade, 1981). Observations under an electron microscope finally settled this dispute by demonstrating the distinct membrane set that constitutes the Golgi apparatus: flattened cisterns and associated vesicles/vacuoles corresponding to the reticular structure observed at the light microscopic level (Dalton and Felix, 1954; Farquhar and Rinehart, 1954; Sjöstrand and Hanzon, 1954).

Subsequent analyses clarified that the organelle plays a pivotal role in the processing and sorting of both soluble and transmembrane proteins passing through the secretory pathway (Farquhar and Palade, 1981, 1998; Marsh and Howell, 2002; Martinez-Alonso et al., 2013). During sequential transition in the stacks of Golgi cisterns, luminal proteins and lipids are modified by the action of Golgi-resident enzymes, including glycosylation (Moremen et al., 2012), sulfation (Huttner, 1988; Niehrs et al., 1994), and proteolytic processing (Halban and Irminger, 1994). Upon post-translational modification and processing, the proteins are sorted at the trans-Golgi network (TGN), the exit site of the Golgi apparatus, for their appropriate destinations such as the plasma membrane via secretory tubulovesicles, secretory granules, and lysosomal/endosomal compartments (De Matteis and Luini, 2008; Farquhar and Palade, 1998; Griffiths and Simons, 1986; Mellman and Simons, 1992). On the other hand, Golgi-resident enzymes are retained in the Golgi apparatus. Membrane-bound glycosyltransferases and other modifying enzymes that function in the Golgi apparatus are excluded and/or removed from membrane carriers forwarding to the secretory pathways (Allan and Balch, 1999; Glick et al., 1997; Opat et al., 2001; Pelham, 2001; Puthenveedu and Linstedt, 2005; Storrie, 2005). In any case, the incessant traffic of tubulovesicular carriers that move along microtubules both in antero- and retro-grade directions largely affect the organization of the Golgi apparatus (Brownhill et al., 2009; Cole and Lippincott-Schwartz, 1995).

Because the flattened cisterns of the Golgi apparatus are stacked in order forming a cup-like or hemispherical shape in exocrine cells that secrete a large amount of proteins in a polarized manner, the fundamental configuration of the Golgi apparatus has been widely accepted as a cup-like/hemispherical shape. Cisterns at the convex and concave faces of the cup-like Golgi stacks are designated as cis- and trans-cisterns that functionally face the rough endoplasmic reticulum (ER) and cell surface, respectively (Farquhar and Palade, 1981; Mellman and Simons, 1992). This organization of the Golgi stacks can explain the vectorial movements of secretory products from the rough ER to their final destinations at the cell periphery.

On the other hand, diversity in the higher organization of the Golgi apparatus depending on the cell/tissue type has been recognized by various microscopic techniques. In the drawings of the earliest studies by light microscopy, the overall shape of the Golgi apparatus is not described as cup-like, but rather a spheroidal network, even in the original drawings of neurons by Golgi (Golgi, 1898a,b). The ultrastructural characteristics and diversities of the three-dimensional architecture of the Golgi apparatus were extensively demonstrated by Rambourg and his colleagues by stereograms of a pair of tilted images from high voltage transmission electron microscopy (Clermont et al., 1995; Rambourg and Clermont, 1997, 1990; Rambourg et al., 1993, 1992, 1981). Through their comprehensive observation and later detailed studies with the aid of computerized tomographic reconstruction (Marsh, 2005; Marsh et al., 2004; Mogelsvang et al., 2004), the higher level organization of the Golgi apparatus is now accepted as a continuous ribbon-like structure in various configurations with compact and non-compact regions. Compact regions consist of piled stacks of Golgi cisterns with convex (cis-) and concave (trans-) sides that are linked to each other by a sparse tubular network defined as the non-compact region (Klumperman, 2011; Rambourg and Clermont, 1990). Observations of osmium-macerated specimens under a high resolution scanning electron microscope has also revealed the diversity of the overall three-dimensional ultrastructure of the Golgi apparatus in various mammalian cells (Koga and Ushiki, 2006; Tanaka and Fukudome, 1991; Tanaka and Mitsushima, 1984; Tanaka et al., 1986). However, the profound mechanisms that promote structural diversity of the Golgi apparatus in vivo remain to be solved.

To shed light on this issue, our review focuses on the structural characteristics of the Golgi apparatus and microtubule network in pituitary gonadotropes, and attempts to illustrate the significance behind the distinctive organization. We also discuss the putative crosstalk between gonadotropin-releasing hormone (GnRH) signaling and the functional molecules that maintain the Golgi organization, based on structural changes of the Golgi apparatus after stimulation of gonadotropes. In parallel, the putative links between cellular polarity and Golgi organization will be discussed by comparing the overall shape and intracellular location of the Golgi apparatus in gonadotropes with those in other endocrine and exocrine cells. The unique organization of the Golgi apparatus in pituitary gonadotropes possibly provides a clue to clarify the theoretical background behind the diversity of the overall shapes of the Golgi apparatus depending on the cell type.

2. Structural characteristics of the Golgi apparatus and microtubule network within rat pituitary gonadotropes

As shown in our recent studies, pituitary gonadotropes generally contain a Golgi apparatus with a globular shape (Fig. 1A and B) in which the outer and inner surfaces are cis- (the entry side of the Golgi) and trans- (the exit side) faces, respectively (Fig. 1C–E) (Koga and Ushiki, 2006; Watanabe et al., 2012). Immunocytochemical localizations of BiP (indicative of rough ER; Fig. 1C) and γ-adaptin (indicative of vesicles generated from the TGN; Fig. 1E) indicate that the pre- and post-Golgi compartments in gonadotropes are mostly segregated from each other by the spherical walls of Golgi cisterns.

The overall shape of the Golgi apparatus in gonadotropes was demonstrated at the light microscopic level about a hundred years ago by staining with the silver impregnation method, although these earlier observations have been often disregarded. The shape of the Golgi apparatus in basophilic gonadotropes of the anterior pituitary has been described principally as round, which spherically enlarges after castration (Addison, 1917; Ellison and Wolfe, 1934; Severinghaus, 1937, 1933; Wolfe and Brown, 1942). Although the circular profile of the globular Golgi apparatus can be observed in electron micrographs of early studies focusing on pituitary gonadotropes (Farquhar and Rinehart, 1954; Kurosumi and Oota, 1968; see also chapter 4 "Gonadotropes" in Costoff, 1973), little attention has been paid to the significance of its globular shape.

To realize the significance of the globular configuration of the Golgi apparatus in pituitary gonadotropes, the intracellular organization of the microtubule network should be considered because the positioning, orientation, and overall configuration of the Golgi apparatus are largely determined by the balance of membrane input and output transported via microtubule-dependent motor proteins (Allan et al., 2002; Brownhill et al., 2009; Cole and Lippincott-Schwartz, 1995; Lippincott-Schwartz, 1998; Murshid and Presley, 2004; Thyberg and Moskalewski, 1999). As described in our recent study, a pair of centrioles immunolabeled with anti-γ-tubulin antibodies is situated at the center of the spheroidal Golgi apparatus as a microtubule-organizing center (MTOC) (Fig. 1B and F) from which radiating microtubules extend in all directions toward the cell periphery through gaps in the spheroidal