Clathrin/AP-2-Dependent Endocytosis: A Novel Playground for the Pharmacological Toolbox?

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Abstract Endocytosis is a vital process for mammalian cells by which they communicate with their environment, internalize nutrients, hormones, or growth factors, or take up extracellular fluids and particles. The best studied among the various pathways to ingest material from the extracellular side is clathrin/AP-2-mediated endocytosis. The past several years have allowed us to gain unprecedented molecular insights into the role of the heterotetrameric AP-2 adaptor complex as a central protein–protein and protein–lipid interaction hub at the plasmalemma. During the initial stages of clathrin-coated pit formation, AP-2 interacts with phosphoinositides and cargo membrane proteins as well as with a variety of accessory proteins and...
clathrin to coordinate clathrin coat polymerization with membrane deformation and cargo recruitment. In addition, a growing list of alternative adaptors provides opportunity for clathrin-dependent cargo selective pathways of internalization and endosomal sorting. Many of these interactions are now understood in structural detail and are thus amenable to pharmacological interference. In this review we will summarize our present state of knowledge about AP-2 and its partners in endocytosis and delineate potential strategies for pharmacological manipulations.

1 Introduction

Endocytosis is a collective term summarizing a variety of different processes by which eukaryotic cells take up extracellular material including fluids, particles, hormones and growth factors, or ligand-bound receptors. In mammalian cells a variety of mechanisms of uptake have been described (Conner and Schmid 2003). These include pinocytosis, phagocytosis, as well as clathrin-dependent and -independent pathways of endocytosis. Pinocytosis (cell drinking) refers to the uptake of fluids by invagination of the plasma membrane. This is followed by the formation of vesicles in the cell soma. Phagocytosis (“cell eating”) is a process whereby large particles are enveloped by the plasma membrane into a so-called phagocytic cup, which is then internalized to form a phagosome (Mukherjee et al. 1997). Clathrin-independent endocytic pathways may involve lipid microdomains presumably in cooperation with membrane integral scaffolding proteins, which have been postulated to form hairpin-loop structures in the cytosolic leaflet of the membrane bilayer. Prime examples are caveolar uptake of glycosphingolipids and flotillin-1-mediated endocytosis of cholera toxin (Glebov et al. 2006). These membrane-organizing scaffolds have been the subject of excellent recent reviews (Morrow and Parton 2005; Bauer and Pelkmans 2006).

By far the best-characterized internalization route is clathrin- and adaptor-dependent endocytosis (clathrin-mediated endocytosis; CME). In this pathway transmembrane cargo including nutrient or signaling receptors as well as synaptic vesicle proteins (Galli and Haucke 2004; Schweizer and Ryan 2006) are endocytosed into clathrin-coated vesicles (CCVs) that bud from phosphatidylinositol 4,5,-bisphosphate (PIP2)-enriched sites at the plasma membrane (Krauss and Haucke 2007; Di Paolo and De Camilli 2006) and deliver their cargo to the endosomal system for recycling or degradation. Examples include receptor-mediated uptake of transferrin, epidermal growth factor (EGF), or LDL. As clathrin, itself a heteromeric stable complex comprising three heavy and three regulatory light chains forming a triskelion structure (Kirchhausen 2000), is unable to associate with the plasmalemma, it requires adaptor proteins that recruit clathrin to “endocytic hot spots” and stimulate lattice or coat assembly. Among these the most important adaptor is the hetetrotetrameric AP-2 complex. AP-2 is also crucial to select cargo and to recruit accessory proteins (Robinson and Bonifacino 2001), some of them functioning as cargo and/or clathrin adaptors themselves. Thus, AP-2 and other monomeric adaptors (collectively termed clathrin-coat-associated sorting proteins, CLASPs; Traub 2005) bridge the gap between the outer