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Review

# Cellular uptake of steroid carrier proteins—Mechanisms and implications

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ABSTRACT

Steroid hormones are believed to enter cells solely by free diffusion through the plasma membrane. However, recent studies suggest the existence of cellular uptake pathways for carrier-bound steroids. Similar to the clearance of cholesterol via lipoproteins, these pathways involve the recognition of carrier proteins by endocytic receptors on the surface of target cells, followed by internalization and cellular delivery of the bound sterols. Here, we discuss the emerging concept that steroid hormones can selectively enter steroidogenic tissues by receptor-mediated endocytosis, and we discuss the implications of these uptake pathways for steroid hormone metabolism and action *in vivo*.



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## 1. Introduction: endocytosis mediates cellular uptake of cholesterol

All sterols transported in plasma or extracellular fluids are solubilized by proteins. When contemplating mechanisms how to deliver circulating sterols to cells, it may be quite insightful to consider how this task is achieved for the prototype sterol cholesterol.

Transport of cholesterol in the extracellular space is facilitated by a special protein complex called lipoprotein (Havel and Kane, 2001). Lipoproteins are spherical macromolecules of 10–1200 nm diameter composed of a core of neutral lipids (mostly cholesterol ester and triglycerides) surrounded by an amphipathic shell of polar phospholipids and cholesterol. Embedded in the shell of lipoproteins are apoproteins that are essential for assembly of the particles and for their recognition by cells (Havel and Kane, 2001). Lipoproteins traffic cholesterol from the tissue of origin to target sites where the lipid cargo is delivered through receptor-mediated endocytosis (Fig. 1) (Goldstein et al., 2001). Delivery involves lipoprotein receptors on the surface of the cells that bind the apoprotein. Following interaction at the cell surface, receptor–ligand complexes are internalized and delivered to endosomal compartments. There, the receptors discharge their cargo. Un-liganded receptors recycle back to the cell surface while lipoproteins move to lysosomes where they are catabolized. The apoprotein moiety is degraded into small peptides and the lipids are released (Goldstein et al., 2001). Cholesterol enters the cellular membrane pool via the endoplasmatic reticulum, is converted into steroid hormones in mitochondria, or stored as cholesterol esters in cytoplasmic lipid droplets (Fig. 1). The exact mechanism of cholesterol trafficking between cellular compartments is still a matter of investigation (Prinz, 2002). Trafficking critically depends on the activity of intracellular sterol carrier proteins that solubilize the sterol and direct its transport (Liu, 2009). For example, exit of cholesterol from lysosomes requires the activity of two proteins designated Niemann-Pick disease type C protein 1 (NPC-1) and 2 (NPC-2). NPC-1 is a polytopic membrane protein with sterol-sensing domain that acts as cholesterol transporter

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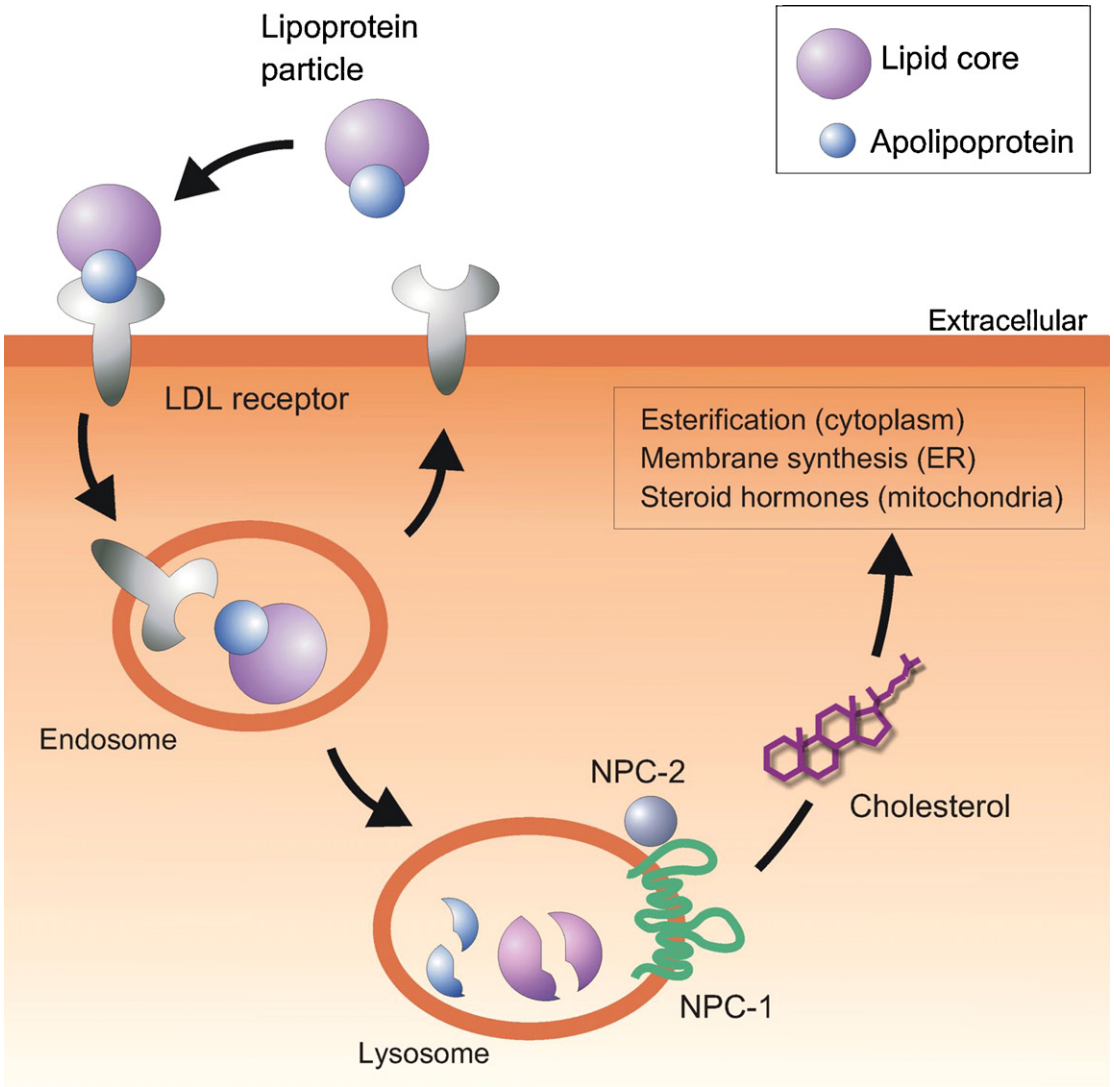


**Fig. 1.** Endocytic pathway for uptake of cholesterol. Lipoproteins are taken up by lipoprotein receptors (LDL receptor) via binding of the apolipoprotein moiety on the lipoprotein particle. Following coated-pit endocytosis, the receptors discharge their ligands in endosomes before recycling back to the cell surface. Internalized lipoproteins are catabolized in lysosomes. There, apoproteins are degraded, while cholesterol enters the cellular membrane pool via the endoplasmatic reticulum (ER), is converted into steroid hormones in mitochondria, or stored as cholesterol esters in cytoplasmic lipid droplets. Exit of cholesterol from lysosomes requires the activity of Niemann-Pick disease type C protein 1 (NPC-1) and NPC-2.

across membranes (Kwon et al., 2009; Zhang et al., 2001). NPC-2 is a small cholesterol binding protein possibly involved in shuttling sterols between membranes (Naureckiene et al., 2000; Okamura et al., 1999).

The composition of apoproteins provides a unique signature of individual lipoprotein classes specifying the origin and types of lipids transported, and their destiny. Target cells express a unique set of lipoprotein receptors on their surface that are able to discriminate various lipoprotein species by recognition of their specific apoprotein profile. Thus, receptor-mediated endocytosis provides an efficient and highly selective mechanism for directing cholesterol and other lipids into their proper target tissue.

The main class of lipoprotein receptors is a group of cell surface proteins called the low-density lipoprotein (LDL) receptor gene family (Fig. 2) (Beffert et al., 2004; Herz and Hui, 2004; Schneider, 2007; Willnow et al., 1999). Family members are expressed in many tissues in organisms as distantly related as nematodes and mammals. The LDL receptor is the archetype of the gene family and has a structure and function typical of a receptor involved in cellular cholesterol uptake (Fig. 2). Its significance for systemic cholesterol homeostasis is underscored by pathological features in patients with familial hypercholesterolemia, inheritable LDL receptor gene defects that result in an inability of affected individuals to clear cholesterol-rich lipoproteins from the circulation (Goldstein et al., 2001). Other members of the gene family with confirmed roles in lipoprotein metabolism include the LDL receptor-related protein (LRP) 1, a receptor for clearance of dietary lipids in the liver (Rohlmann et al., 1998). Very low-density lipoprotein (VLDL) receptors and yolkless are expressed in oocytes of egg-laying species from insects to birds and mediate the endocytic uptake of yolk (Bujo et al., 1995; Grant and Hirsh, 1999; Schonbaum et al., 1995).

## 2. Receptors for steroid carriers – surface binding sites for sterol signaling and uptake

In contrast to the precursor cholesterol, cholesterol-derived steroid hormones are not transported by lipoproteins but by plasma carrier proteins. Carrier proteins are unique for individual classes of steroid hormones. They include the vitamin D binding protein (DBP; the carrier for vitamin D metabolites) (White and Cooke, 2000), the sex hormone-binding globulin (SHBG; the carrier for androgens and estrogens) (Hammond and Bocchinfuso, 1995), and