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Review

The role of cholesterol in rod outer segment membranes

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Abstract

The photoreceptor rod outer segment (ROS) provides a unique system in which to investigate the role of cholesterol, an essential membrane constituent of most animal cells. The ROS is responsible for the initial events of vision at low light levels. It consists of a stack of disk membranes surrounded by the plasma membrane. Light capture occurs in the outer segment disk membranes that contain the photopigment, rhodopsin. These membranes originate from evaginations of the plasma membrane at the base of the outer segment. The new disks separate from the plasma membrane and progressively move up the length of the ROS over the course of several days. Thus the role of cholesterol can be evlauated in two distinct membranes. Furthermore, because the disk membranes vary in age it can also be investigated in a membrane as a function of the membrane age. The plasma membrane is enriched in cholesterol and in saturated fatty acids species relative to the disk membrane. The newly formed disk membranes have 6-fold more cholesterol than disks at the apical tip of the ROS. The partitioning of cholesterol out of disk membranes as they age and are apically displaced is consistent with the high PE content of disk membranes relative to the plasma membrane. The cholesterol composition of membranes has profound consequences on the major protein, rhodopsin. Biophysical studies in both model membranes and in native membranes have demonstrated that cholesterol can modulate the activity of rhodopsin by altering the membrane hydrocarbon environment. These studies suggest that mature disk membranes initiate the visual signal cascade more effectively than the newly synthesized, high cholesterol basal disks. Although rhodopsin is also the major protein of the plasma membrane, the high membrane cholesterol content inhibits rhodopsin participation in the visual transduction cascade. In addition to its effect on the hydrocarbon region, cholesterol may interact directly with rhodopsin. While high cholesterol inhibits rhodopsin activation, it also stabilizes

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the protein to denaturation. Therefore the disk membrane must perform a balancing act providing sufficient cholestrol to confer stability but without making the membrane too restrictive to receptor activation. Within a given disk membrane, it is likely that cholesterol exhibits an asymmetric distribution between the inner and outer bilayer leaflets. Furthermore, there is some evidence of cholesterol microdomains in the disk membranes. The availability of the disk protein, rom-1 may be sensitive to membrane cholesterol. The effects exerted by cholesterol on rhodopsin function have far-reaching implications for the study of G-protein coupled receptors as a whole. These studies show that the function of a membrane receptor can be modulated by modification of the lipid bilayer, particularly cholesterol. This provides a powerful means of fine-tuning the activity of a membrane protein without resorting to turnover of the protein or protein modification.

Keywords: Cholesterol; Rhodopsin; Rod outer segment; GPCR

Contents

1. Introduction

Cholesterol is an essential membrane constituent of most animal cells. This sterol has been shown to be involved in a wide variety of critical cell functions, including modulation of enzyme function, permeability, fusion and receptor function. Because of its importance to normal membrane function, the mechanism of cholesterol action in biological membranes has been the focus of intensive investigation for decades. Not surprisingly, it is now clear that cholesterol exerts complex, multifaceted effects on cellular membranes. The critical importance of cholesterol to normal functioning of cell membranes may lay in its ability to both alter fundamental properties of the phospholipid bilayer and to interact directly with specific membrane proteins. This duel role of cholesterol was described in a review by Yeagle in 1991 [1]. In this review, the complex effects of cholesterol were used to explain the correlation between optimal protein function and the