Regulation of Membrane Fluidity in Cold Environments

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Temperature changes and periods of detrimental cold occur frequently for many organisms in their natural habitats. Homeothermic animals have evolved metabolic adaptation strategies to increase mitochondrial-based energy expenditure and heat production, largely relying on fat as a fuel source. Alternatively, certain species are able to repress their metabolism during cold periods and enter a state of decreased physiological activity known as torpor. By contrast, poikilotherms, which are unable to maintain their internal temperature, predominantly increase membrane fluidity to diminish cold-related damage from low-temperature stress.

lipid metabolism cold adaptation membrane fluidity mitochondria

1. Introduction

Environmental cold causes multiple challenges for organisms. Generally, low temperature slows down the rate of molecular processes and enzyme activities that are essential for survival. Organisms have evolved different adaptation strategies for cold environments. They either increase thermogenesis to keep their core temperature constant (are endothermic) or they are unable to actively regulate their internal temperature and take on the ambient temperature (are ectothermic). Organisms with a variable internal temperature have developed protective physiological adaptative responses to survive in cold conditions. For both cold survival strategies, namely, active temperature regulation through thermogenesis and physiological adaptation due to a variable internal temperature, alterations in lipid metabolic processes, including lipid catabolism and membrane fluidity regulation, are essential.

By increasing their lipid-dependent energy expenditure, homeothermic animals, such as mammals, are able to maintain their core body temperature during cold exposure. Lipids are primarily stored in the adipose tissue in homeotherms and serve as metabolic fuel. To preserve their core body temperature in cold environments, homeothermic animals oxidize lipids in mitochondria predominantly in their brown adipose tissue. During this process, referred to as non-shivering thermogenesis, the chemical energy stored in lipids is utilized to generate heat in mitochondria via uncoupling proteins, which uncouple the electron transport from the respiratory chain [1][2]. When seasonal temperatures are decreasing, several orders of mammals are able to lower their internal temperature (become heterothermic) and hibernate. Hibernating animals have evolved metabolic strategies to preserve energy and decrease their core body temperature to enter an energy-saving torpid state, which results in metabolic repression and a shift from carbohydrates to lipid catabolism [3][4].

Homeothermic organisms predominantly adjust their metabolism to seasonal changes. However, poikilotherms, which have a variable internal temperature according to the ambient temperature, are affected by diurnal temperature fluctuations. Diurnal temperature changes are metabolically challenging, especially for small poikilotherms or microorganisms. They have evolved physiological adaptation processes primarily for their membranes. In poikilotherms, the membrane lipid composition is altered to maintain the optimal membrane fluidity critical for the proper function of membranes in low-temperature conditions [5][6][7]. Such a conservation process of the physiological state of membranes in cold environments is known as homeoviscous adaptation and was first identified in bacteria [8]. In addition, homeoviscous adaptation enables low-temperature survival of poikilothermic species, including nematodes and flies [5][6][9]. It typically leads to an increase of unsaturated fatty acids in membrane phospholipids, which promotes membrane fluidity and counteracts the membrane rigidifying effects of cooling. However, changes in membranes that increase their fluidity are complex and also depend on the fatty acid composition, their chain length and modifications of their head groups [10].

2. Regulation of Membrane Fluidity in Poikilothermic and Cold-Adapted Organisms

A reduction in the environmental temperature has a pronounced effect on the physical properties of membranes, their functions and, ultimately, on the survival of poikilotherms. Membrane lipid bilayers are predominantly fluid at physiological temperatures, which is critical for normal cellular functions [11]. During a temperature decrease, membrane bilayers can change from a disordered fluid to a gel-like non-fluid state [12]. In the non-fluid condition, saturated fatty acyl chains of phospholipids are in a closely packed, ordered arrangement. Consequently, during cold exposure, an excess of saturated fatty acids (SFAs) in phospholipids rigidifies the membrane due to their straight acyl chains, which are stabilized by hydrophobic interactions [13]. Higher-ordered fatty acyl chains are usually in their fully extended conformation, which increases the thickness of the fatty acyl chain area and the distance between polar head groups of the bilayer [14][15][16]. Therefore, a reduced membrane fluidity can result in an elevated membrane thickness under low-temperature conditions. To maintain fluidity and thickness of the bilayer in an optimal range, poikilothermic organisms have developed response mechanisms that can activate lipid desaturases to convert SFAs to unsaturated fatty acids (UFAs). Lipid desaturases introduce double bonds in fatty acids [17], which generate kinks into otherwise straightened acyl hydrocarbon chains of phospholipids. Such double bonds, especially *cis*-double bonds, result in looser packing and increased fluidity of membrane bilayers to maintain their biological functions following temperature downshifts.

Adaptive processes that regulate membrane function were predominantly studied in mesophilic organisms, which prefer to grow at moderate temperatures in a range from 20 °C to 45 °C. However, special adaptation strategies have been evolved by microorganisms thriving in permanently cold ecosystems, the deep sea, and polar or glacial habitats. Such organisms, known as psychrophiles (“cold-loving” organisms), prefer an optimal growth temperature at ~15 °C or below [18] and are often exposed to diurnal temperature changes and repeated freeze and thaw cycles in terrestrial environments. Therefore, they have evolved remarkable strategies to maintain their membrane function under extreme temperature conditions. Physiological adaptations of membranes to cold were

comprehensively studied in psychrophilic microorganisms. Psychrophilic bacteria and cyanobacteria increase the proportion of UFAs and short-chain fatty acids (SCFAs) in their membranes [10]. In addition, the head groups of phospholipids and the membrane content of branched-chain fatty acids (BCFAs) are modified to adapt to permanently cold habitats. UFAs are generated by de novo fatty acid (FA) synthesis. Alternatively, double bonds can be introduced into SFAs after their biosynthesis [11], which enables a rapid response to temperature downshifts. Swift desaturase-based membrane modifications are also employed by psychrotolerant bacteria, which have an optional growth temperature of 20 °C to 25 °C but can survive at temperatures below 0 °C [18][19].

Double bonds are usually introduced into fatty acids in a *cis*-configuration by desaturases. UFAs in phospholipids with double bonds in a *cis*-configuration elevate membrane fluidity more efficiently than *trans*-UFAs because the *cis*-configuration results in an immobile 30° kink in the acyl chain [20][21]. The kink causes steric hindrance within fatty acid chains and interferes with the lateral packing of acyl chains in the lipid bilayer. Certain psychrophilic and mesophilic Gram-negative bacteria can regulate an isomerization from the *cis*- to the *trans*-configuration of double bonds in UFAs through a periplasmic enzyme known as *cis–trans* isomerase (Cti) [22][23]. The substrate binding of the isomerase appears to be determined by membrane properties controlling the access of the Cti enzyme to its *cis*-FA substrates located in the inner membrane of Gram-negative bacteria [23]. At low temperatures, the membrane fluidity is reduced, which counteracts an intrusion of Cti into the membrane. However, when the temperature increases and membranes become more fluid, Cti might penetrate the inner membrane bilayer and catalyze the *cis–trans* isomerization of acyl chains. This results in an increase in *trans*-UFAs, which have properties that resemble SFAs and align more closely with each other. Thus, *trans*-UFA generation elevates the viscosity of the membrane to ensure membrane functionality at higher temperatures. The *cis–trans* conversion enables a fast adaptive response (e.g., during diurnal temperature upshifts) and can be employed under growth-inhibiting stress conditions when the fatty acid composition cannot be changed by de novo synthesis [24].

In addition to their acyl chain properties, phospholipids affect the physical state of membranes through their head groups [10][25]. The head groups of diverse phospholipids have different sizes and charges and their acyl chains are differentially modified, which influences the packing and fluidity of the bilayer. In a previous study in yeast using shotgun lipidomics, it was found that *Saccharomyces cerevisiae* alters the proportion of phospholipids in the membrane when exposed to cold [26]. The degree of unsaturation of acyl chains is dependent on the phospholipid class under low-temperature conditions. Such a head-group-specific acyl chain remodeling was recently observed in the Gram-negative bacterium *Methylobacterium extorquens*, which has a relatively simple membrane lipid composition [27]. Following cold exposure of *M. extorquens*, the phospholipids phosphatidylcholine (PC) and phosphatidylethanolamine (PE) display the most pronounced changes in unsaturation. Moreover, the amount of PC lipids in the bacterial membranes increases, whereas PE lipids are reduced during cold conditions. A diminished PE level might counteract the effect of an elevated packing density due to a strong interaction between PE lipids in bacterial membranes [25][27][28]. Conversely, a higher PC content likely improves membrane fluidity at lower temperatures, suggesting that the modulation of phospholipid levels is essential for membrane adaptation in cold.

Psychrophilic bacteria isolated from permanently cold habitats, such as sea ice or arctic glaciers, upregulate the proportion of SCFA and BCFA in their membranes [29][30]. An increase in SCFAs and BCFAs was detected in

psychrophilic strains of *Bacillus cereus*, a foodborne pathogen, which can grow in refrigerated food at 4 °C [31]. Short acyl chains of phospholipids do not reach as far into the hydrophobic area of the membrane bilayer as longer acyl chains do. Therefore, shorter chains, especially chains with less than 12 carbons, form weaker hydrophobic interactions with proteins and other lipids, which increases the motion of free acyl chain ends and promotes membrane fluidity in cold environments [32][33]. Contrary to the swift acyl chain remodeling based on desaturation or *cis–trans* isomerization, the incorporation of SCFAs is coupled to bacterial growth because it requires de novo synthesis of fatty acids [32]. De novo synthesis of lipids is also essential for Gram-positive bacteria to upregulate certain BCFAs in response to cold [34]. Methyl branches on BCFAs are predominantly located at the penultimate (*iso*-) or antepenultimate (*anteiso*-) position of fatty acid chains. *Anteiso*-fatty acids in phospholipids have a more pronounced membrane-fluidizing effect than *iso*-fatty acids. The methyl branch in *anteiso*-fatty acids is located further from the end of the fatty acid, which efficiently reduces the packing order of phospholipids' acyl chains in the membrane bilayer [11]. Psychrotolerant Gram-positive bacteria, such as *Listeria monocytogenes*, increase the proportion of *anteiso*-BCFA and decrease the amount of *iso*-BCFA in the membrane to promote membrane fluidity in response to low growth temperatures [35][36][37]. The regulation of BCFA is species- and temperature-dependent and an upregulation of *iso*-BCFAs is also observed in Gram-positive bacteria when exposed to low-temperature stress [34][38]. Many psychrophilic or psychrotolerant bacteria can replace saturated longer and *iso*-BCFAs with unsaturated shorter and *anteiso*-BCFAs to reduce membrane rigidity as a cold adaptation strategy. Similar responses to cold, namely, an increase in UFAs, SCFAs and BCFAs in membranes, were observed for mesophilic bacteria as well, suggesting that both mesophilic and psychrophilic bacteria appear to share common mechanisms to promote membrane fluidity.

Certain psychrophilic organisms modify their membrane phospholipid pool by increasing the amount of lysophospholipids (LPLs), which are altered phospholipids (PLs) lacking one of their acyl chains. Antarctic psychrophilic yeast strains naturally synthesize increased levels of lysophosphatidylethanolamine (LPE) and lysophosphatidylcholin (LPC) compared with mesophilic yeast *S. cerevisiae* [39]. Membrane LPLs can be generated via hydrolysis of an acyl chain in PLs through the enzymatic activity of phospholipases as part of the de-acylation/re-acylation cycle (Lands' cycle [40]) or via de novo synthesis of PLs. LPLs were found in membranes of animals in relatively low quantities, e.g., in insects only around 1% of total PLs are LPLs [41][42]; however, their proportion can increase during cold exposure. LPLs have an inverted conical shape and hence disrupt the packing order of PLs' acyl chains in membranes, which increases membrane fluidity [9]. Elevated LPL levels were detected in *Drosophila* in response to low temperatures and during cold acclimation [41][43]. In addition, LPLs are upregulated during seasonal acclimatization of the bug *Pyrrhocoris apterus* [42]. These studies suggest that LPLs are essential components in membranes for shaping thermal responses. The specific functions of LPLs in cold adaption have only been studied in a small number of organisms so far and are still poorly understood, but might be relevant for cold-related responses of many species in their natural habitats.

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