Ecophysiology of Omega Fatty Acids: A Lid for Every Jar

Omega fatty acids affect various physiological functions, such as locomotion, cardiac function, and thermogenesis. We highlight evidence from animal models that points to pathways by which specific omega fatty acids exert differential effects. We suggest that optimizing the omega fatty acid composition of tissues involves trade-offs between costs and benefits of specific fatty acids.

Omega fatty acids (FA), also called polyunsaturated FA (PUFA), are important precursors of membrane phospholipids and eicosanoid hormones, and act directly as signaling molecules (66). Omega FA contain two or more double bonds in their fatty acyl chain and are subdivided into omega-3 and omega-6 FA, according to the location of the first double bond with reference to the terminal methyl group. Mammals cannot synthesize omega FA de novo since they lack the necessary enzymes as opposed to many ectotherms and plants (reviewed in Ref. 20). Thus the two essential omega FA, omega-6 C 18:2 [linoleic acid (LA)] as well as the omega-3 C 18:3 [alpha linolenic acid (ALA)] must be obtained from the diet and are also referred to as “essential fatty acids” (EFA). Physiologically, the effects of the two EFA and of their chain-elongated and further desaturated derivatives can be very different. For instance, although omega-6 FA are metabolized to pro-inflammatory, yet very important prostaglandins, certain omega-3 FA are considered potent anti-inflammatory agents. A plethora of beneficial functions for human health have been attributed to omega FA, in particular to the highly unsaturated omega-3 C 22:6 [docosahexaenoic acid (DHA); Ref. 20]. These include positive effects on the cardiovascular system, anti-inflammatory effects, and beneficial effects for neural function. The role of omega FA in human health aspects has been thoroughly reviewed in the past (4, 36, 67, 84) and is not the focus of this contribution. We instead will discuss current knowledge on important effects of omega FA on physiological functions in animals, particularly their role in temperature and seasonal acclimatization. Although our focus is on mammals, we collate information from a variety of organisms, such as birds, reptiles, or fishes, to highlight common mechanisms.

Omega FA Effects on Muscle Function and Metabolism

Compensation of suppressed enzymatic activity at low temperature is of pivotal importance for hibernating mammals, and omega FA play an important role herein. When kept during the preceding summer on a diet rich in omega-6 FA, namely LA, hibernators exhibit longer torpor bouts, lower minimum body temperatures (T_b), and hence less energy expenditure during winter (reviewed in Refs. 79, 99; see Figure 1 for an example of the typical course of T_b in a hibernator during winter). This has been attributed to positive effects of certain omega-6 FA on Ca^{2+} handling in cardiomyocytes during hypothermia (see below). A high concentration of omega-6 FA in phospholipids (PL), in this case specifically LA, was found to increase the activity of the membrane sarcoplasmic reticulum Ca^{2+} ATPase (SERCA) (108), the rate-limiting membrane pump that removes Ca^{2+} from the myocyte cytosol during each contraction (88).

At present, it is unknown whether similar temperature compensation of SERCA activity exists in skeletal muscle, since this tissue contains a different SERCA isoform in fast-twitch fibers (89). Candidates for investigating this question are muscles of nonhibernating mammals operating in the body’s periphery at lower T_b during winter (9, 10, 23, 63, 111), and, of course, muscle from ectothermic organisms exposed to low temperature, e.g., muscles generating sound at high frequencies such as sonic muscles on the toadfish (Batrachoididae) swim-bladder or the rattlesnake (Crotalinidae) rattle muscles. However, increased SERCA activity and hence muscle contractibility may be responsible for the positive correlation between omega-6 content of PL and maximum running speed, found in a comparison of 36 mammal species (101) (Figure 2), for increased treadmill endurance and work capacity of rats feed a diet high in omega-6 FA (12), and for enhanced exercise performance in a flight wheel reported for two migratory songbird species (92, 94). Furthermore, the capacity of muscle for nonshivering thermogenesis (NST) could be improved if membranes are rich in omega-6 FA. Muscle cells can generate heat without contraction by futile cycling of Ca^{2+} across the SR membrane, a mechanism long known from the heater organ of billfish (18). SERCA uses only part of the chemical energy derived from ATP hydrolysis to transport Ca^{2+} across the membrane; the rest is dissipated as

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heat. A recent study on a knockout mouse model detected an important regulatory role of sarcolipin in this process, i.e., its ability to promote uncoupling of the pump, leading to excessive ATP-hydrolysis and heat production (13). In a second route, the hydrolysis of ATP is even completed before Ca\textsuperscript{2+} transport and all the energy derived from ATP hydrolysis is converted into heat (37). SERCA-mediated NST is presumably most important for animals with limited or lacking brown adipose tissue, such as large mammals, marsupials, and birds. Altogether, omega-6 FA as promoters of SERCA activity could play a so far overlooked central role in thermoregulation.

In contrast to omega-6 FA, omega-3 FA suppress SERCA activity (50, 108) but seem to have positive effects on pathways delivering ATP. The long-chain omega-3 FA are particularly important because key enzymes of the Krebs cycle and β-oxidation are known to have higher activity in skeletal muscle in birds and mammals having high concentrations of Docosapentaenoic acid (DPA; omega-3 C22:5) or DHA in their diet (75, 76, 80, 93, 121). In line with these results, physical exercise in humans increases the concentration of DHA in skeletal muscle PL and decreases the ratio of omega-6 to omega-3 FA (6, 59). Furthermore, thermogenic capacity of hibernators (Marmota marmota) increases during the course of hibernation along with an increase of DPA and DHA in PL (8). This could result from improved NST in brown adipose tissue with high DHA-content in PL (102) but also from improved SERCA-mediated NST, since uncoupled SERCA activity is more pronounced at high ATP-to-ADP ratios (38).

Omega FA effects on membranes have also been invoked to explain differences in another important physiological characteristic of animals, their basal metabolic rate. The “membrane pacemaker hypothesis of metabolism” (reviewed in Ref. 62) was based on the observation that smaller mammals with higher mass-specific metabolic rate also have more highly unsaturated membranes (in particular, higher omega-3 DHA content) than larger animals (34). In addition, investigating isolated cell organelles revealed that ectotherms such as reptiles have lower cellular respiration rates than mammals, while possessing lower contents of omega-3 FA, especially DHA (21). However, several tests of the “membrane pacemaker hypothesis of metabolism” gave reason to doubt this idea: no relationship was found between muscle omega FA content (or DHA content) and basal metabolism in a dataset of 30 mammalian species when body mass was taken into account (115). In addition, intraspecific studies failed to confirm that variation in membrane lipid composition was associated with differences in basal metabolic rate (25, 54).

Omega FA or their metabolites can also affect gene expression as ligands for peroxisome proliferator-activated nuclear receptors (PPARs; Refs. 19, 66). The isomers PPARα and PPARγ stimulate fatty acid oxidation, PPARγ lipogenesis (16, 44). At least for PPARα, it was shown that long-chain omega FA, namely eicosapentaenoic acid (EPA; C20:5 n-3), and DHA are high-affinity ligands, in contrast to saturated long-chain FA (11, 55). There are, however, apparent species-dependent differences in the ligand-binding specificity and affinity of PPARs.
among mammals (17, 87). Beyond these findings, the specificity of different PUFAs as activators of PPARs is still a matter of debate and ongoing research (19, 66, 91). Because of their general effect on lipid metabolism, PPARs were suspected to be the target of increased omega-3 FA uptake in certain migratory birds, resulting in improved muscle performance (reviewed in Ref. 121). However, a subsequent experimental study on quails (Colinus virginianus) failed to support this view (80).

The Hibernating Heart

As outlined above, omega FA seem particularly important for the adaptation of tissues and organs to changing temperature. This adaptation is crucial in the case of the hearts of hibernating mammals, which have to maintain circulation by sustaining cardiac muscle contractions even at a tissue temperature of ~1°C. During hibernation, heart rate drops to 3-10 beats/min, compared with 200–400 beats/min when the animal is active (74). At $T_b$ below 20°C, the vast majority of mammals experience cardiac arrest due to severe arrhythmias and ventricular fibrillation (26, 31, 73, 118). Conversely, hibernator hearts show a high resistance to ventricular fibrillation (65) and remain in sinus rhythm at a $T_b$ approaching 0°C (26, 28, 74).

Several factors and mechanisms have been proposed to explain resistance to ventricular fibrillation and to account for continued heart function at low $T_b$. These include a short duration of QT intervals (35), i.e., the time between the electrical depolarization and repolarization of the ventricles, an increase in gap junctions facilitating synchronous cardiac contraction (43, 103), and lower adrenergic innervation of the heart (for review, see Ref. 65).

Enhanced Ca$^{2+}$ handling within the cardiomyocytes is probably the most important adaptation of the hibernators’ heart (reviewed in Refs. 72, 119). Ca$^{2+}$ entry into cardiomyocytes is regulated in part by L-type calcium channels (LTCCs). This influx of Ca$^{2+}$ provides the trigger to release sarcoplasmic reticulum (SR) Ca$^{2+}$ stores into the cytoplasm of the cardiomyocyte via opening of the ryanodine receptor, thus inducing cardiac contraction (42) (FIGURE 3). Hibernators downregulate the entry of Ca$^{2+}$ into myocytes through ion channels and simultaneously upregulate Ca$^{2+}$ removal into intracellular storage compartments, i.e., the SR. In hibernating ground squirrels and hamsters, the volume of longitudinal SR in myocytes is two to three times larger than in summer-acclimated individuals (15, 73, 98, 110). Furthermore, in hibernating woodchucks, mRNA and protein levels of SERCA in cardiomyocytes were increased threefold compared with animals in the nonhibernating season. Simultaneously, hibernating woodchucks showed a 50% reduction in both mRNA and protein levels of the SERCA inhibitor phospholamban (123). An upregulation of gene expression of SERCA and reduced levels of phospholamban expression were also found in hearts of hibernating ground squirrels (22).

The activity of the transmembrane pump SERCA is particularly affected by the FA composition of the surrounding PL (108, 109). Recently, Giroud et al. (50) provided the first evidence for specific roles of certain omega-6 and omega-3 FA in the regulation of cardiac SERCA activity during hibernation. SERCA activity was strongly positively associated with LA content and negatively correlated with the amount of DHA in cardiac SR PL of torpid Syrian hamsters (FIGURE 3). Also, very high amounts of DHA in the SR PL were found in individuals that failed to hibernate (cf. Ref. 60). Using path analysis, Giroud et al. (50) found specific causal relations between the FA composition in the SR membrane, SERCA activity, and $T_b$ of the animals: Differences in proportions of both LA and DHA in the SR membrane were associated with altered SERCA activities, which in turn determined the minimum $T_b$ reached by the animals during torpor. These effects of omega FA on heart function at low temperature are probably specific for hibernating endotherms, because in most ectotherms myocardial contractions do not require Ca$^{2+}$ release from the SR. Instead, in these species, contraction is initiated exclusively by Ca$^{2+}$ influx through L-type Ca$^{2+}$ channels (LTCC) (cf. FIGURE 3) located in the sarcolemma (review in Ref. 105).

One focus of further research on hibernating endotherms could be the effects of specific omega FA on the time hibernators can remain torpid before they need to rewarm. Whereas protein degradation may not be entirely blocked at low $T_b$ (116), synthesis of proteins, including SERCA, is drastically downregulated during torpor entry and only resumed during arousals (29, 117). Thus a high LA content could partially compensate for a reduction in SERCA activity resulting from proteolysis over time, prolonging the time hibernators can remain torpid until the need to synthesize SERCA protein forces them to rewarm.

Remodeling of Membranes

Since omega FA are essential, their concentration in WAT and plasma reflects the availability of PUFA in the diet and can vary considerably (1, 7, 24). Furthermore, there is ample evidence that dietary intake of PUFA also influences the PL FA composition of membranes in mammals and birds (e.g., Refs. 5, 75, 76, 80, 114), an effect that is apparently more pronounced in hibernators or species expressing daily torpor than in homeothermic
species (45, 46). However, the direct effect of diet on membranes seems to be remarkably low compared with the effect on WAT and plasma, as found in an extensive feeding experiment in rats in which even the balance of omega-6 and omega-3 FA in PL was hardly altered (1). Only very low concentrations (≤10%) of omega-3 FA in the diet, i.e., presumably an undersupply, led to correspondingly low concentrations of these FA among PUFA in PL. Therefore, the existence of a homeostatically regulated balance of omega-6 to omega-3 FA with organ-specific set-points seems likely (61). However, PL FA composition in various tissues is subject to endogenously and photoperiodically controlled seasonal change in hibernators (8), daily heterotherms (47, 48), and even humans (39). In addition, the PL FA composition of membranes in humans and rats can vary on a daily basis (124) and as a result of physical exercise (Refs. 6, 58; humans, Ref. 59; rat Refs. 77, 112).

Model of Ca\(^{2+}\) handling in cardiomyocytes of hibernators

Model of Ca\(^{2+}\) handling in cardiomyocytes of hibernators (modified from Ref. 99). Contraction of myofilaments is caused by Ca\(^{2+}\) release from the sarcoplasmatic reticulum (SR) through ryanodine receptor channel proteins (RyR), following depolarization of the cell membrane and Ca\(^{2+}\) entry through L-type Ca\(^{2+}\) channels (LTCC). During hibernation, rapid Ca\(^{2+}\) reuptake into the SR is enhanced by increased expression of SERCA (the SR Ca\(^{2+}\) ATPase) and decreased expression of the SERCA inhibitor phospholamban (black arrows). Phospholamban, in turn, is regulated by protein kinase A (PKA), Ca\(^{2+}\)/calmodulin-dependent protein kinase II (CaMKII), and protein phosphatase 1 (PP1) (not shown). SERCA activity during hibernation is additionally increased due to high linoleic acid (LA) and low docosahexaenoic acid content (DHA) in phospholipids of the surrounding SR membrane. The enlarged cartoon of SERCA shows the principal domains of the Ca\(^{2+}\) pump. The transport of two Ca\(^{2+}\) ions per cycle into the SR involves strong conformational changes in the transmembrane domains, which is affected by the fatty acid composition of the bilayer.
increasing unsaturation, and for a given number of double bonds, it decreases with increasing chain length (96). De novo synthesis of phosphatidylethanolamine (PE) and phosphatidylcholine (PC), the most abundant PL in mammals, yields primarily four molecular species (16:0–18:1, 16:0–18:2, 18:1–18:2, 16:0–22:6) (49, 104). About 50% of PC is remodeled in a deacylation/reacylation process known as the Lands cycle (125).

Although previous work suggested that the acyltransferase enzymes catalyzing the deacylation/reacylation process do not discriminate well between omega-3 and omega-6 FA (68), this view has been revised. For instance, substrate-specific reacylation is assumed for multiple forms of lysophosphatidylcholine acyltransferases (LPCAT). LPCAT3, an isoform recently found in the endoplasmic reticulum of cultured human cell lines, prefers unsaturated fatty acyl-CoAs as substrates with highest affinity to linoleoyl-CoA (18:2) (125). Expression of the protein, examined with quantitative PCR, was most pronounced in human liver, pancreas, and adipose tissue (125). Another candidate responsible for enrichment of membranes with omega-6 FA, in this case arachidonic acid (AA, 22:4 n-6), a derivative of essential LA, is the glycerol-3-phosphate acyltransferase 1 (GPAT1). GPAT1 is found in the outer mitochondrial membrane and catalyses the common first step of triglyceride and PL synthesis. Unlike other GPAT isoforms, GPAT1 esterifies preferentially palmitate (16:0) at the sn-1 position of the glycerol-3-phosphate. In the absence of GPAT1 activity, the 16:0 content is lower in PC and PE, and accompanied by substantial enrichment of AA and a decrease of DHA at the sn-2 position (32, 122). Since GPAT1 mRNA is known to decrease and increase with fasting and refeeding, respectively, it could well be a mechanism contributing to the profound accumulation of omega-6 FA into PL, found in alpine marmots before hibernation and their removal after termination of hibernation in spring (8).

Another important pathway is the conversion of PE to PC via three methylation reactions by phosphatidylethanolamine-N-methyltransferase (PEMT) in the liver (97). This pathway could be significant with respect to omega FA, because PC synthesized via PEMT are enriched with DHA at the sn-2 position (95). Therefore, it has been suggested that the PEMT pathway plays an important role in the transport of DHA from the liver to the plasma and other tissues (95, 120). In vertebrates, one tissue that is particularly enriched in PL containing DHA is the brain. A candidate for a specific DHA transporter is the transmembrane protein Mrsd1a, a member of the major facilitator superfamily, which is highly expressed in endothelial cells of blood vessels in the brain. Mrsd1a removes DHA from circulating, albumin-bound lysophosphatidylcholine-DHA (which can be derived from PC by phospholipase A2) and transfers it to the brain-facing side (82).

So far, no evidence exists for omega-6 or omega-3 specificity of other prime candidates for membrane remodeling like plasma membrane FA binding proteins, FA translocase (FAT/CD 36), intracellular FA binding proteins, and FA transporter proteins (41).

**Molecular Effects of Omega Fatty Acids in Membranes**

Omega FA are thought to exert many physiological functions by being constituents of glycerophospholipids, which are a major component of cell membranes (FIGURE 4). Proteins that are known to be affected by the composition of the lipid bilayer include rhodopsin, Na⁺-K⁺-ATPase, cytochrome c oxidase, and SERCA (3, 69–71, 78, 83, 90). Many insights on protein membrane interactions are based on biochemical and biophysical studies of artificial membranes (review in Ref. 70).

Transmembrane proteins undergo conformational changes that perturb the surrounding lipid bilayer. The composition of solvent lipids that surround the protein, also called annular lipids (FIGURE 4), affect the energy required to deform the bilayer during protein conformational changes (3, 70, 90). One determinant of these kinetic changes is hydrophobic mismatch, that is, the degree to which the hydrophobic transmembrane

**FIGURE 4. Function of a membrane protein**

The function of a membrane protein (green) may be affected by numerous properties of the surrounding lipid bilayer. Phospholipids in the bilayer consist of a polar headgroup (blue) and two fatty acyl chains (pink). Proteins are affected by headgroups [such as phosphatidylcholine (PC), phosphatidylethanolamine (PE), phosphatidylserine (PS), and others] as well as fatty acyl chains, which may be saturated or unsaturated. Both of these factors determine numerous properties of the membrane that affect conformational changes of proteins.
domain of the protein is matched to the hydrophobic thickness of the membrane (40, 64). Mismatch causes local stretching or compression of the bilayer, or even of the protein (69) (FIGURE 4). For several membrane proteins, it has been shown that their activity depends on the fatty acyl chain length of the bilayer (e.g., Ref. 14, 53, 107), which could be one mechanism by which PL composition, in particular changes in long-chain omega FA content, exert effects on membrane-embedded proteins.

Membrane proteins, including SERCA, are also affected by PL head groups (FIGURE 4). Increasing the content of PE significantly increases the activity and Ca$^{2+}$ affinity of SERCA, and PL headgroups also affect, for instance, rhodopsin (3, 53, 69, 70). The interaction of PL headgroups with membrane proteins is governed not only by the headgroup itself but also by the fatty acyl chains, particularly their degree of unsaturation, which alters the area the headgroup occupies in the bilayer surface (81). Hence, omega FA may indirectly regulate transmembrane proteins via effects on PL headgroup properties. PL with different headgroups also differ in their tendency to form curved rather than planar phases. In biological membranes, these lipids are forced, however, to assume a normal planar bilayer, which creates so-called curvature frustration or curvature stress (52) (FIGURE 4). This represents a source of energy stored in the bilayer that will also affect conformational changes of membrane proteins.

One of the oldest hypotheses on the mechanisms by which omega FA alter the properties of membrane proteins is related to their effect on bilayer fluidity (or its inverse, viscosity). In natural omega FA, double bonds in a cis configuration create kinks in the fatty acyl chain, which, as FA move and rotate, decrease order and increase fluidity of the bilayer (FIGURE 4). The observation that many microorganisms, plants, ectothermic animals, and even hibernating mammals respond to changes in tissue temperature by modifying membrane PL composition in a way that, at least partly, maintains membrane fluidity even in the cold gave rise to the “homeoviscous adaptation” hypothesis (2, 33, 56, 106). This hypothesis postulates that organisms adjust membrane properties under changing environmental conditions to maintain optimal viscosity. However, the validity of this hypothesis, at least as a single, universal mechanism of membrane adaptation, has been questioned (reviewed in Ref. 56). Furthermore, as outlined in detail by Lee (69), altering the PL composition changes the equilibrium properties of conformational changes in both SERCA and rhodopsin, an effect that, based on thermodynamics, cannot be attributed to viscosity.

Yet another property of membranes that has been invoked to explain their regulatory effect on proteins are lateral pressure profiles (e.g., Ref. 27). The lateral pressure profile arises from depth-dependent changes in stress inside the bilayer caused by hydrophobic, electrostatic, and steric interactions, which may affect membrane proteins. This pathway could be important to understand omega FA effects, because the lateral pressure profile is significantly altered by the degree of membrane unsaturation (e.g., Ref. 30, 86). Also, experiments with constant chain length PC bilayers have shown that SERCA activity was in fact dependent on the degree of unsaturation (53).

There is one further mechanism by which omega FA-containing PL (or other lipids, such as cholesterol or sarcosine) may regulate membrane proteins, namely direct binding of lipids with protein domains, especially in grooves between transmembrane $\alpha$-helices (review in Ref. 70). These so-called non-annular lipids (FIGURE 4) may be important regulators of diverse proteins and protein complexes. For instance, simulations of molecular dynamics indicate that DHA-containing lipids form tight associations with specific locations in the core of rhodopsin, modifying helix-helix interactions (51). Also, SERCA apparently requires the presence of PE between two specific $\alpha$ helices for proper conformational changes (85). Obviously, these direct actions of non-annular lipids and the effects of bilayer properties outlined above are not mutually exclusive and may even be synergistic.

Conclusions

Omega FA are involved in acclimatization of organisms to both environmental changes and endogenous shifts in physiological states, particularly temporal changes in tissue temperature. The current evidence points to specific physiological functions of specific omega FA rather than to ubiquitous effects, such as membrane fluidity, that were the focus of earlier work on this subject. The different effects of omega-6 and omega-3 FA on membrane-bound enzymes hint at intriguing molecular conflicts. For instance, the positive effects of LA on SERCA and cardiac function during hibernation is likely non-adaptive for summer-active animals, which explains rapid remodeling of membranes. Hence, there probably is no optimal “all-purpose” omega FA composition of tissues, which creates a trade-off between costs and benefits of each FA. Exploring solutions for these trade-offs resulting from natural selection for different ecological situations and life history stages should be an intriguing field of future research.
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