- include sources of omega-3 fats (see Box);
- be high in fibre; and
- offer generous amounts of vegetables and fruits, whole grains, and low fat dairy foods.

Adulthood — treatment

Cholesterol-lowering with plant sterols

- Margarines enriched with plant sterols should be considered for patients with increased cardiovascular risk factors, in whom low-density lipoprotein level reduction is desirable.
- Phytosterol-containing foods are valuable additions to other cholesterol-lowering treatments, including statins.
- Encourage the consumption of an additional serving of carotenoid-rich fruit or vegetable (eg, rockmelon, mangoes, carrots, pumpkin) to overcome the possible reduction in some carotenoids in plasma.

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Background

The renaissance of fat: roles in membrane structure, signal transduction and gene expression

Gareth S Denyer

Summary

- The intracellular and intramembrane profiles of fatty acids mirror those of dietary fat intake.
- The properties of transporter and receptor proteins embedded within cell membranes are influenced by the composition of the phospholipid membrane of cells.
- Many cell-signalling pathways involve lipids or lipid-derived molecules.
- Specific fatty acids are increasingly being identified as key regulators of gene expression and tissue differentiation.

IN RECENT YEARS, it has become clear that fat has a role beyond that of macromolecular energy storage. Indeed, fat participates in intracellular processes as diverse and complex as membrane fluidity, signal transduction and the regulation of gene expression. Furthermore, as specific fats are involved in mediating these effects, the profile of dietary intake assumes vital importance, especially as humans cannot make several of the key lipids themselves.

Fatty acids and membrane function

All cell membranes consist of a bilayer of phospholipids. The membrane is impermeable to charged molecules, so, for communication between cells and compartments to occur, specific protein transporters or receptors have to be embedded in the bilayer. The bilayer is fluid and flexible, allowing free lateral movement of the proteins and the formation of invaginations to permit the processes of endocytosis and exocytosis.

Crucially, the length and degree of saturation of the fatty acids in the membrane phospholipids determines the fluidity of the membrane. Long (> 16 carbons) and saturated fatty acyl groups tend to make the membrane less fluid, whereas shorter, unsaturated fatty acids permit greater flexibility and permeability. The functionality of proteins in the membrane is critically dependent on membrane fluidity, especially when the proteins have to collide with other molecules to exert their effects (as in many receptor-mediated pathways) or when the proteins have to be endocytosed (such as the ingestion of low-density lipoproteins [LDLs] after binding to the LDL-receptor).

It is vital that a variety of fatty acids be available for membrane phospholipid construction. Many of the fatty acids in membranes are unsaturated and cannot be made by humans *de novo*. These include alpha-linolenic acid and linoleic acid. Therefore, the mix of fatty acids in the diet can have profound effects on the membrane phospholipid fatty acid composition and on the efficiency of membrane-mediated processes. For example, the ability of insulin to communicate its signal is strongly impaired when animals are fed a diet high in saturated fat and this effect can be overcome with omega-3 poyunsaturated fatty acid intake. This, in turn, is probably related to diet-induced changes in membrane fatty acid profile, as recent studies have shown strong correlations between membrane phospholipid composition and insulin sensitivity in humans.[1]

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Fatty acids and signal transduction

Sometimes the phospholipids themselves participate in signalling pathways. For example, some activated receptors stimulate phospolipases that cleave phospholipids into the head group and diacylglycerol. Both these moieties can subsequently activate other downstream signalling molecules — either within the membrane itself or in other compartments. For example, the cleavage of the phospholipid glycerolipid phosphatidylinositol (PI) gives rise to inositol *tris*-phosphate (which can cause the release of calcium into the cytoplasm), and diacylglycerol (which activates the enzyme protein kinase C to stimulate several mitogenic and metabolic signalling cascades).[2] As before, the fatty acyl composition of the diacylglyerols involved in the above signalling pathways is strongly influenced by the diet.

Other processes involving cleavage of membrane lipids include the production of prostaglandins, prostacyclins, thromboxanes and the precursors of platelet-activating factors. The key point, however, is that all these pathways are dependent on having a suitable pool of membrane fatty acids as substrates, and, although some remodelling of membrane fatty acyl composition can occur,[3] the diet is the strongest modulator of intracellular lipid profiles. Indeed, dietary lipid composition can itself affect the activity of the enzymes that control the fatty acid composition of membranes.[3]

Fatty acids and gene expression

The expression of genes is regulated by a class of DNA-binding proteins called transcription factors. The latter can be regulated by binding to other proteins, or, as has recently emerged, to fatty acids.[4,5] Some of the most-studied lipid-regulated transcription factors are those which regulate adipocyte gene expression and differentiation. For example, the physiological ligands for one of these factors, peroxisomal proliferator-activated receptors (PPARs), are omega-6 and omega-3 fatty acids and related eicosanoid products,[6] and this provides a direct link between dietary fatty acid consumption, tissue proliferation and gene expression. In addition, the expression of many lipogenic enzymes is controlled by other transcription factors (eg, sterol regulatory element binding protein [SREBP1]).[7] SREBP1 is a membrane-bound protein that is activated after cleavage and release from the membrane — and this is influenced by the fatty acyl composition of the signalling and membrane components. Recently, it has become obvious that these transcription factors are just part of a large superfamily of nuclear receptors which respond to specific fatty acid messengers.[8]

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