Editorial

Trans-Fatty Acids and Sudden Cardiac Death

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A relationship between diet and human disease has been known at least since the time of Hippocrates. Our “modern” understanding of the role of nutrition in heart disease began in 1908, when a diet of meat, milk, or eggs was found to produce atherosclerosis in rabbits; a decade later, cholesterol was identified as causing the experimental lesions. Epidemiological studies that began in the 1930s confirmed this correlation in humans, but the importance of diet in causing atherosclerosis attracted little attention until the 1950s, when a high intake of saturated fats was recognized as a major risk factor for myocardial infarction and stroke. Although the role of dietary lipids in causing vascular disease is now established, an influence of fat intake on cardiac arrhythmias is less well-appreciated. The potential importance of this relationship is highlighted by Lemaitre et al. who in this issue of Circulation, suggest that dietary trans-fatty acids cause sudden cardiac death. Trans-fatty acids differ from the natural cis-isomers in the configuration around the double bond; in the former, the fatty acyl chains are on opposite (trans) sides of the molecule, whereas they are on the same (cis) side in the latter. Most dietary trans-fatty acids are formed when unsaturated fats are “hardened” by hydrogenation and when vegetable oils become hydrogenated during frying; they occur in hardened margarines, fast foods, and some commercially baked goods and salad dressings.

The possibility that dietary lipids cause cardiac arrhythmias became apparent more than 30 years ago when the severity of ventricular arrhythmias in patients after myocardial infarction was found to correlate with elevated circulating levels of free fatty acids (FFA). These observations stimulated experimental studies that confirmed that FFA can be arrhythmogenic, especially when catecholamine levels are high. Clinical studies also showed a direct relationship between high FFA levels, arrhythmias, and sudden cardiac death. The arrhythmogenic potency of these lipids is determined not only by the amounts that reach the heart, but also by their structure; for example, the ability of different FFA to lower ventricular fibrillation threshold depends on the length and saturation of the fatty acyl chain. A role for FFA intake has been shown in experimental animals, where diets rich in polyunsaturated fats and fish oil were found to have antiarrhythmic effects. Clinical studies also suggest that a diet rich in fish oil and other unsaturated FFA can prevent cardiac death and arrhythmias, although not all published data support the importance of this relationship.

The mechanisms underlying the pro- and antiarrhythmic effects of FFA are readily explained by their interactions with biological membranes, which are lipid bilayers made up of 2 hydrophilic (lipophobic) surfaces and a hydrophobic (lipophilic) core (Figure). The latter, which is virtually impermeable to charged molecules, contains the fatty acyl chains of the membrane lipids, whereas the 2 surfaces are lined with charged head groups that interact with the aqueous media on either side of the membrane. Most biological activities are mediated by proteins imbedded in the bilayer; these include enzymes, receptors, carriers, pumps, and the voltage-gated ion channels responsible for the cardiac action potential. The bilayer was once viewed simply as a supporting structure for the membrane proteins, much as a sea whose surface can float a variety of ships. It is now apparent, however, that hydrophobic portions of membrane proteins interact specifically with lipids within the core of the bilayer. This specificity is one reason why changes in membrane composition, as occur when FFA and other lipophilic molecules are incorporated into the bilayer, alter such functions as opening, closing, and inactivation of ion channels.

A likely mechanism by which dietary fat intake might influence cardiac rhythm became apparent in the 1970s, when the hydrophobic surfaces of intrinsic membrane proteins were recognized to interact with hydrophobic regions of the surrounding bilayer lipids. These lipids, initially viewed as a long-lived annulus, are now known to exchange readily with lipids elsewhere in the membrane. The functional importance of hydrophobic surfaces on the membrane-spanning a-helices of membrane proteins is underscored by evidence that the binding sites for many drugs and physiological ligands, even ions that are transported across membranes, include these transmembrane segments. Hydrophobic interactions with membrane proteins allow FFA, whose hydrocarbon tails are readily incorporated in the bilayer, to exert remarkably specific effects on membrane function. Using as a model the effects of various FFA on calcium pump of rabbit skeletal muscle sarcoplasmic reticulum, we not only found that increasing fatty acyl chain length and the extent of unsaturation potentiated inhibition of calcium transport, but also that the response to many FFAs was highly dependent on the
functional state of the calcium pump. These and other findings demonstrate a high specificity for the hydrophobic interactions between membrane lipids and membrane proteins (Figure) and so provide a plausible explanation for the ability of different dietary fatty acids to exert specific effects on ion channel function.

A correlation between primary cardiac arrest and high membrane content of trans-fatty acids is documented by the population-based case-control study reported by Lemaitre et al., which found that the trans-fatty acid content of erythrocyte membranes obtained from survivors of out-of-hospital cardiac arrest was greater than that in membranes from age- and sex-matched controls. Membrane levels of trans-fatty acids in this study did not correlate with such "traditional" risk factors for atherosclerosis as age, sex, hypertension, diabetes, or smoking, but were lower in high school graduates than nongraduates; the latter finding suggests that the healthy lifestyle choices associated with education include avoidance of foods that contain trans-fatty acids. Although an earlier case-control clinical study found no correlation between sudden cardiac death and adipose tissue content of trans-oleic and trans-linoleic acids, there is substantial evidence that trans-fatty acid intake is associated with increased coronary heart disease risk.

Although currently available data do not prove that trans-fatty acids cause sudden death, the findings of Lemaitre et al. fit with other data supporting an important link between dietary fat intake and arrhythmias. In view of solid evidence that the lipids we ingest find their way into our membranes, where some can do a great deal of harm, it seems prudent to minimize the intake of foods that contain a high content of trans-fatty acids.

References


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