LETTER

Docosahexaenoic acid ethyl esters ineffective?

Recently in PNAS, Hoshi et al. (1) report the results of elegant studies defining the molecular basis for the blood pressure-lowering effect of omega-3 fatty acids, in particular docosahexaenoic acid (DHA). They found that DHA, when infused intravenously, activated the large-conductance Ca^{2+}- and voltage-activated K^+ (BK) channels in vascular smooth muscle but that the infusion of DHA ethyl esters (like those contained in dietary supplements) failed to activate BK channels. The authors indicated that their findings have "practical implications for the use of omega-3 fatty acids as nutraceuticals for the general public and also for the critically ill receiving omega-3–enriched formulas."

This conclusion is unwarranted. With regard to implications for critically ill patients receiving omega-3–enriched intravenous emulsions, Hoshi et al. (1) state that "These emulsions, which are available for enteral as well as for parenteral (central venous) application, may result in administration of up to 10 g of DHA/EPA per patient per day and may contain either free or ester-conjugated omega-3 fatty acids [citing Marik and Zaloga (2)]." In fact, none of these products contains free fatty acids, and the authors may not have understood that "ester-conjugated" does not refer to esterification with ethanol (i.e., ethyl esters) but with glycerol as triglycerides (oils). When infused intravenously, the triglyceride-bound fatty acids in emulsified fish oils are hydrolyzed from the glycerol backbone by lipoprotein lipase, an endothelial enzyme, releasing the fatty acids for uptake into various tissues where they become incorporated into cellular lipid pools. Consequently, the findings of Hoshi et al. have no implications for critically ill patients since neither free fatty acids nor ethyl esters are found in intravenous lipid emulsions.

Neither are there implications for "the general public." There are many encapsulated omega-3 ethyl ester products on the market, both pharmaceuticals (Lovaza, GlaxoSMithKline; Vascepa, Amarin; Epadel, Mochida; Omacor, Pronova) and dietary supplements, all designed for oral, not intravenous, use. During digestion, they are converted into free fatty acids by the action of pancreatic lipases that remove the ethanol moiety. The now nonesterified (free) fatty acids are absorbed into the enterocyte and reesterified into phospholipids, triglycerides, and/or cholesterol esters. These are then incorporated into chylomicrons, which are secreted into the lymphatic system, ultimately enter the bloodstream through the thoracic duct, and are then distributed to various tissues, including endothelial and smooth muscle cells in the vasculature. Therefore, the vasculature is never exposed to omega-3 ethyl esters. Hence, the findings of Hoshi, et al., although true in their unique experimental settings, have no relevance to intravenous fish oil emulsions or to dietary supplements and have quite limited "practical implications."

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1 Hoshi T, et al. (2013) Omega-3 fatty acids lower blood pressure by directly activating large-conductance Ca^{2+}-dependent K^+ channels. *Proc Natl Acad Sci USA* 110(12):4816–4821.

2 Marik PE, Zaloga GP (2008) Immunonutrition in critically ill patients: A systematic review and analysis of the literature. *Intensive Care Med* 34(11):1980–1990.

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