Is it time to separate EPA from DHA when using omega-3 fatty acids to protect heart and brain?

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Support for high intakes of the bioactive omega-3 fatty acids (FAs), EPA and DHA, for decreasing risks of cardiovascular diseases (CVD) began almost four decades ago. This was initiated by the publication of studies on Greenland Inuits, trials investigating effects on CVD risk factors and then the DART and GISSI-Prevenzione secondary prevention trials [1]. However, "negative" trials followed, leading to controversies as to the benefits of omega-3 FAs in the prevention of both coronary heart diseases and stroke [2]. A 2018 Cochrane Library systematic review concluded that overall EPA and DHA have little or no effect for primary or secondary prevention of cardiovascular diseases [3]. Most clinical trials and reviews assessing the effects of omega-3 FAs in CVD and other conditions reported on combinations of EPA and DHA for the experimental interventions. With the recent publication of the strongly positive results of the REDUCE-IT trial [4] on the effects of a high dose of an ethyl ester of EPA (no DHA included) there has been a renewed enthusiasm for using omega-3 FA to prevent and treat CVD affecting both heart and brain [5]. The findings of REDUCE-IT also highlight the question as to whether EPA might be more effective than DHA in preventing and/or treating CVD.

Over the past fifteen years there has been increasing evidence that EPA and DHA are associated with different clinical and molecular effects. As one example, a number of studies and reviews have suggested that EPA is more effective than DHA in the treatment of depressive mood disorders [6]. Furthermore, a number of recent publications now detail differences between EPA and DHA on how they affect plasma lipids and lipoproteins, endothelial function and hemodynamics, platelet function and coagulation, blood pressure and heart rate responses, glycemic control, as well as other factors related to CVD [7-9].

REDUCE-IT and the earlier JELIS study (Japan EPA Lipid Intervention Study) [10] provide a basis for considering EPA to be more effective than DHA in the reduction of cardiovascular morbidity and mortality. REDUCE-IT reported the effects of 4 grams daily of icosapentyl ethyl, essentially an ethyl ester of EPA, on reduction of primary and secondary cardiovascular end points [4]. The decreases both in coronary heart disease and stroke related endpoints generally ranged between 22% – 28%. JELIS provided 1.8 grams of EPA, but no DHA, as an ethyl ester per day, and showed benefits in secondary prevention after myocardial infarction with, for example, a 19% reduction in repeat coronary events over a mean 4.6 years duration of follow up [10]. Of note, JELIS was carried out in Japan in a population with a high baseline intake of omega-3 FAs. Subsequently, negative trials using combinations of EPA and DHA diminished enthusiasm for the JELIS results [2, 3]. However, since the REDUCE-IT trial results were released, there has been markedly increased interest in the possibility of wider use of omega-3 FAs in the prevention and management of CVDs. Of note, both JELIS and REDUCE-IT enrolled subjects who were on statins. The combination of EPA with statins may be particularly relevant to the positive outcomes of both these trials as discussed below.

While supplements containing higher proportions of EPA compared to DHA seem to be more effective in treating depression, there have been a number of studies suggesting that higher levels of DHA may be associated with reduced risk of developing all-cause dementia [11]. Using rodent models of stroke, recent studies have shown that acute injection of DHA as a free fatty acid or in a triglyceride emulsion is far more effective than EPA in decreasing brain cell death and preserving neurofunction after stroke [12-14]. Similar benefits for DHA versus EPA are reported for anti-inflammatory effects in an experimental model of spinal cord injury [15].

The clinical and animal model studies described above raise the question as to whether we should be studying specific omega-3 FAs (i.e. EPA and DHA) to differentially target disorders relating to the heart and to the brain. There are also emerging possibilities on the use of a third bioactive long chain omega-3 fatty acid, docosapentaenoic acid (DPA), in the prevention and treatment of CVD [9].

Over the period that the inconsistent results of clinical trials with omega-3 FAs have been published, there has been evolving interest in defining the molecular differences between EPA and DHA at structural, functional, and cell biological levels [16-20]. Studies on artificial membranes, as well as on cells and organelles using techniques such as NMR and X-ray diffraction, have uncovered major differences between the behavior of EPA and DHA in cell membranes [17, 18]. As an example, DHA has substantially greater effects than EPA on affecting membrane permeability and increasing membrane fluidity, as well as structure/function changes associated with dissolution of sphingomyelin/cholesterol lipid rafts [17]. Important to atherosclerosis and coronary artery disease, EPA strongly inhibits glucose–related membrane cholesterol crystalline domain formation; this is related to its antioxidant effects [21]. Indeed, EPA also has more potent antioxidant effects than does DHA in a number of systems such as oxidation of lipoproteins. Of interest to the outcome of both the JELIS and REDUCE-IT trials, where all subjects were on statins, is that the antioxidant effects of EPA in vitro were substantially enhanced in the presence of statins [22] . In contrast, in studies in Dr. Deckelbaum's laboratory, acute injection of DHA after hypoxic ischemic stroke injury in mouse models was far more effective than EPA in decreasing overall brain tissue levels of lipid and

protein derived oxidation products, and had much stronger effects in decreasing ROS production in the ipsilateral part of the brain exposed to hypoxic-ischemic injury [13, 14]. Acute DHA injection was much more effective than EPA in decreasing post-stroke infarct size and in preserving neurofunctional outcomes in mice eight weeks after the initial hypoxic-ischemic injury, with no additional omega-3 FA supplementation after the initial post-stroke treatment [13, 14].

EPA and DHA are "parent" molecules for the production of specialized pro-resolving mediators (SPMs), a group of potent autocoids which are classified as protectins, resolvins and maresins. SPMs derived from DHA and EPA have some similar, but also many different effects on inflammatory and post-inflammatory resolution pathways and cell death mechanisms [23, 24]. DHA derived mediators are particularly relevant to neuroprotection after stroke in rodent models [14, 23].

Thus, with differences between EPA and DHA in long term supplementation studies as well as in acute therapeutics, might we be entering a new era in how we study and apply the use of omega-3 FAs? As we transition into the next decade of understanding chronic versus acute administration of omega-3 FAs, we also need to continue emphasizing shared and non-shared mechanisms between EPA and DHA. For some conditions, might their combination with non-omega-3 compounds such as statins provide better therapeutic outcomes than the combined use of EPA and DHA? As we further study differences of clinical benefits between the omega-3 FAs, we need to better define the distinct molecular pathways of action of EPA and DHA, and

also DPA. We need to determine what scenarios might benefit from their combined as compared to their individual application.

Disclosure Statements

Dr. Deckelbaum is a founding scientist and member of the scientific advisory board of DeckTherapeutics, Inc., a company developing diglyceride lipid emulsions to prevent tissue death after ischemic organ injuries. Dr. Deckelbaum is an inventor on Columbia University assigned patents on omega-3 rich diglyceride emulsions as potential agents for cytoprotection of different organs after ischemic injury.

Dr. Calder acts as a consultant to Cargill, DSM and Smartfish and has research funding from BASF AS.

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