Stearidonic Acid Raises Red Blood Cell Membrane Eicosapentaenoic Acid\(^1,2\)

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Abstract

The consumption of EPA and DHA has been associated with reduced risk for cardiovascular disease morbidity and mortality. Mean intakes of EPA and DHA in the United States and elsewhere are below levels recommended by health authorities. The main non-marine source of dietary (n-3) fatty acids (α-linolenic acid) is poorly converted to EPA in humans. Stearidonic acid (SDA) is a non-marine fatty acid that appears to be more readily converted to EPA in humans. Results from previous studies suggested that SDA, relative to EPA, increases RBC EPA, with reported efficiencies ranging from ~16 to 30%. A recently published, randomized, single-blind, controlled, parallel group study in healthy men and women characterized the relationships between intakes of SDA and EPA and EPA enrichment of RBC membranes over a 12-wk period. %EPA in RBC membranes was greater after EPA (0.44, 1.3, or 2.7 g/d, respectively) and SDA (1.3, 2.6, or 5.2 g/d, respectively) consumption compared to a safflower control (all \(P < 0.02\)). Based on quadratic response surface models, for EPA intakes of 0.25, 0.50, and 0.89 g/d, SDA intakes of 0.61, 1.89, and 5.32 g/d, respectively, would be required to produce equivalent values for RBC % EPA, translating to relative efficiencies of 41.0, 26.5, and 16.7%. Thus, dietary SDA over a range of intakes increases RBC % EPA, with declining relative efficiency as SDA intake increases. J. Nutr. 142: 626S–629S, 2012.

Introduction

Data from prospective epidemiological studies and randomized controlled trials support an association between intakes of long-chain (n-3) PUFA, specifically EPA and DHA, and reduced risk for cardiovascular morbidity and mortality (1–4). For example, male physicians in the United States consuming fish at least once per week demonstrated a reduction in risk of sudden cardiac death over 11 y of follow-up in the Physicians’ Health Study (5). The Japan EPA Lipid Intervention Study showed that Japanese patients randomly assigned to consume 1.8 g/d of EPA in combination with a statin drug had a 19% reduction in major coronary events after 4.6 y of follow-up compared with those assigned to receiving a statin alone (6). The Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto miocardico-Prevenzione trial showed that a marine oil supplement (~850 mg/d EPA + DHA) resulted in a 15% relative risk reduction compared to usual care for the primary endpoint of death, nonfatal myocardial infarction, and nonfatal stroke over a 3.5-y period (7).

In light of this evidence for cardiovascular benefits, health authorities have recommended increasing dietary consumption of long-chain (n-3) fatty acids by consuming fatty fish at least once to twice per week, which is equivalent to ~250–500 mg/d of EPA + DHA (3,8). However, current intakes are below levels recommended for optimal health in the United States and much of Europe (9,10) (Fig. 1). Barriers to increasing intakes of long-chain (n-3) PUFA include dietary preferences (many people do not like the taste of fish), caution regarding the presence of methylmercury and other contaminants in some fish, concerns regarding sustainability of fish supplies, economic burden, and technical difficulties involved in fortification of foods with EPA and DHA (11). The main non-marine type of (n-3) PUFA, ALA, is poorly converted to EPA in humans, due in part to low activity of Δ6-desaturase, the rate limiting enzyme for conversion (12).

SDA, 18:4(n-3), is a fatty acid produced by desaturation of ALA by the Δ6-desaturase enzyme (11). Although it occurs

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naturally in selected species of fish and plants, it can be substantially increased in soybean oil via genetic modification of soybeans and thus SDA-rich oil can be substituted for traditional oil in food applications (11). Because SDA is downstream from Δ6-desaturase, it is more readily converted to EPA than ALA (12). James et al. (13) conducted one of the first studies in humans to show that dietary SDA is metabolized to EPA. Participants consumed 0.75 g/d of encapsulated EPA, SDA, or ALA as ethyl esters for 3 wk, followed by 3 wk at 1.5 g/d. Levels of long-chain (n-3) fatty acids in RBC have been shown to correlate well with levels in tissues, including epithelial cells and cardiac myocytes, and thus can be used as a biomarker for diet-induced changes in tissue levels of EPA (14,15). No significant increase was observed in RBC %EPA in the ALA group, but significant increases at 3 and 6 wk were observed for the SDA and EPA groups. Similar results were obtained for plasma phospholipid EPA. The results suggested efficiency of SDA consumption of 30%, relative to EPA consumption, for raising RBC or plasma phospholipid %EPA, indicating that 3.3 g/d of SDA would have to be consumed to produce the same effect as 1.0 g/d of EPA. In contrast, the relative efficiency of ALA was 7%; thus, 14.2 g/d of ALA would be required to produce the same effect as 1.0 g/d of EPA. Harris et al. (16) evaluated the conversion efficiency in participants consuming 3.7 g/d SDA from SDA-enriched soybean oil for 16 wk. The relative efficiency of SDA was 16.4% compared to EPA, resulting in a 6.1:1 ratio of SDA:EPA for raising RBC %EPA to the same degree. More recently, Lemke et al. (17) showed that participants consuming 4.2 g/d of SDA as SDA-enriched soybean oil for 12 wk exhibited increased RBC %EPA at a relative efficiency of 17.1% compared to EPA provided as ethyl esters, a ratio of 5.8:1 for SDA:EPA.

**Dose- and Time-Dependent Effects of SDA**

Because results from these earlier studies suggested possible differences in the relative efficiencies of conversion of SDA to % EPA in RBC with increasing dosages, we recently evaluated the effects of a range of SDA and EPA (as encapsulated ethyl esters) intakes on EPA enrichment of RBC membranes in generally healthy men and women. This allowed us to evaluate and compare the dose-response curves for altering RBC %EPA over a 12-wk period.

The methods and results of this trial have been described in detail elsewhere (18). Briefly, participants (n = 137; 15–19/group) were randomized at wk 0 to the control group (safflower oil softgels, Solgar) or one of seven treatment groups (SDA ethyl ester softgels in 0.43-, 1.3-, 2.6-, or 5.2-g/d dosages or EPA ethyl ester softgels in 0.44-, 1.3-, or 2.7-g/d dosages). Safflower oil was selected as the control due to its low ALA content. RBC fatty acid profiles (OmegaQuant) were measured at wk 0, 2, 4, 6, 8, 10, and 12 and the prespecified primary outcome variable was RBC EPA, expressed as a percentage (by weight) of all fatty RBC fatty acids (16).

Mean values for RBC %EPA by group and time point indicate that all dosages of EPA and SDA increased %EPA in RBC membranes relative to control (P < 0.02) at wk 12, with the exception of 0.43 g/d SDA (P = 0.19) (Fig. 2). No significant changes were observed in RBC %DHA, %ALA, or %SDA at the end of the treatment. The %DPA in RBC membranes increased (P < 0.05) in all groups at wk 12 compared to control, except those receiving 0.43 g/d SDA and 0.44 g/d EPA (18).

![FIGURE 1](n-3) fatty acid recommendations and current estimated mean intake levels in selected countries or regions. The boxes represent the recommended ranges of intakes from the organizations specified: AFFSA (22), WHO (23), Dietitians of Canada (24), BSHC (25), AHA (3), ADA (24), EFSA Dietetic Products, Nutrition, and Allergies NDA Panel (10), and EANS (26). European Union intakes were taken from the EFSA NDA Panel (10) and U.S. intakes were taken from NHANES 1999–2002 (27). ADA, American Dietetic Association; AFFSA, French Food Safety Agency; BSHC, Belgian Superior Health Council; EANS, Expert Workshop of the European Academy of Nutritional Sciences; EFSA, European Food Safety Authority; NDA, Dietetic Products, Nutrition, and Allergies.

**FIGURE 2** Percentages of EPA in RBC membranes in healthy men and women consuming control (safflower), 0.44, 1.3, or 2.7 g/d of EPA (A) or 0.43, 1.3, 2.6, or 5.2 g/d of SDA (B) for 12 wk. Data are means ± SEM, n = 137 randomized (n = 14–18/group). *Different from control, P < 0.001. †Different from control, P < 0.05. Figures were created from data presented in (18). SDA, stearidonic acid.
It is notable that RBC %DHA was unchanged by either SDA or EPA consumption. This finding is consistent with the view that conversion of EPA to DHA in humans occurs to a very limited extent (16,17,19). In addition, RBC %SDA remained very low, and below the lower limits of detection for most participants, during SDA consumption. This suggests that most of the SDA consumed is converted to EPA or oxidized (16,17).

Using first-order kinetics, model estimates for the time required to reach one-half the steady-state value for RBC % EPA were 2.30 wk for EPA and 1.75 wk for SDA, and these did not differ significantly. However, the relative efficiencies of SDA and EPA for increasing RBC % EPA were not directly proportional over the full dosage range, suggesting that the formation of EPA from SDA becomes less efficient with increasing SDA intake (18).

Relative efficiencies were 41.0, 26.4, and 16.7% for dietary intakes of 0.61, 1.89, and 5.32 g/d SDA, respectively, based on the results of quadratic surface models. These corresponded to equivalent doses of EPA of 0.25, 0.5, and 0.89 g/d, and SDA:EPA ratios of 2.4:1, 3.8:1, and 6.0:1, respectively. These estimates are very similar to those previously reported, as reviewed above (13,16,17).

At present, it is not clear why incorporation of EPA into RBC membranes after SDA consumption becomes less efficient with increasing SDA dosage. Although the conversion efficiency of ALA to EPA is consistently low, a previous investigation showed that diets high in ALA increase ALA oxidation, thereby reducing its conversion to EPA (20). It remains to be determined whether a similar pattern exists for conversion of SDA to EPA, possibly secondary to saturation of enzymes in the conversion process, or if other mechanisms are involved.

Conclusions and Implications

Several health organizations recommend EPA + DHA intakes of 0.25–0.5 g/d for optimal health (3,8,10,21). Studies examining the effects of SDA consumption on RBC %EPA have shown consistent results (13,16–18) and indicate that intakes of 0.6–1.9 g/d of SDA produce RBC %EPA levels equivalent to those produced by 0.25–0.5 g/d of EPA intake, which can be easily achieved with consumption of SDA-rich oil.

These studies add to the growing body of evidence supporting SDA as an alternative dietary source of long-chain (n-3) fatty acids. Additional research is warranted to assess the potential health effects of SDA oil consumption, particularly with regard to reducing risk for cardiovascular disease.

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