The intake of long chain omega 3 fatty acids through fish versus capsules results in greater increments of their plasma levels

Oléagineux, Corps Gras, Lipides. Volume 11, Numéro 2, 116-7, MARS/AVRIL 2004, Sources

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Summary : Omega 3 fatty acids from fish appear to be more cardioprotective than equivalent amounts provided as capsules. We gave volunteers, for six weeks, either 100 g\\day of salmon, providing 383 mg of EPA and 544 mg of DHA or one or three capsules of fish oil\\day, providing 150 mg of EPA and 106 mg of DHA or 450 mg of EPA and 318 mg of DHA. We also re-evaluated data from a previous study carried out with the same design. Marked increments in plasma EPA and DHA concentrations (µg\\mg total lipid) and percentages of total fatty acids were recorded at the end of either treatment. Such increments were linearly and significantly correlated with the dose after capsule administration. Notably, increments in plasma EPA and DHA concentration after salmon intake were significantly higher than after administration of capsules. In fact, the same increments would be obtained with at least two- and nine-fold higher doses of EPA and DHA, respectively, if administered with capsules rather than salmon. In turn, we provide experimental evidence that omega 3 fatty acids from fish are more effectively incorporated into plasma lipids than when administered as capsules and that increments in plasma concentrations of EPA and DHA given as capsules are linearly correlated with their intakes.

Keywords : omega 3, cardiovascular disease, fish, DHA, EPA

ARTICLE

Several minor components in the diet cannot be synthesized “de novo” in the body but, at the same time, play essential roles in vital processes. These compounds are defined as “nutritionally essential”. Several other types of compounds ingested with the diet are able to modulate biological processes and functions and, therefore, they are endowed with “pharmacological” or, eventually, “toxicological” properties or features.

Food generally consists of animal and plant tissues and organs and, therefore, it provides complete cellular machineries (e.g. enzymes, cofactors, structural components, etc.) rather than pure chemicals. A remarkable exception to this situation is represented by milk, the only type of food in which an array of complex molecules – with primary nutritional roles – is arranged in highly

organized micellar dispersions. This represents a very efficient strategy specifically developed by nature to optimize the delivery of nutrients to rapidly growing and nutritionally demanding organisms, such as those of infants.

The essentiality of the different nutrients and the observation that they may be beneficial for our health have promoted their utilization as "drugs" (or bioactive compounds), frequently without paying attention to optimize the formulation for their delivery. In fact, it is frequent that, in clinical studies, such preparations proved to be less effective than what was predictable from epidemiological data based on the intakes through the diet, e.g. in the case of certain antioxidants. This may apply, to some extent, to several lipid-soluble nutrients which are quantitatively minor components of the diet, such as lipid-soluble antioxidants and minor fatty acids (FA). These compounds are generally ingested together with the bulk of fats, being part of natural foods or food items (oils and fats) derived from them. The independent ingestion of small amounts of lipid soluble compounds dissociated from their natural matrix and often not with regular meals may result in less efficient bioavailability.

In particular, the Western diet provides an average of less than 100 mg/day of the long chain (LC) omega 3 fatty acids EPA (eicosapentaenoic acid, 20:5n-3) and DHA (docosahexaenoic acid, 22:6n-3) – mainly found in fish – out of a total fat intake of about 100 g/day. These minor components have been shown to be protective with respect to various atherogenic factors, on the bases of well documented epidemiological and clinical studies [1, 2].

Various studies have indeed shown that populations consuming fish two-three times/week, i.e. ingesting relatively small amounts of omega 3 FA, are protected when compared with abstainers, although fish intake may provide other protective agents in addition to omega 3 FA. In addition, controlled studies [3] have shown that the intake of fish rich in omega 3 is protective toward cardiovascular events, and that fish is more protective than pharmaceutical preparations providing equivalent amounts of omega 3 fatty acids [4]. The different bioavailability of omega 3 fatty acids taken in food or as capsules, however, has never been explored in details.

Study design

This chapter describes the results of studies that have been previously reported [5], focussing more specifically on the practical implications of the results. We have investigated, in healthy subjects, the relationships between the consumption of either salmon, with given amounts of EPA and DHA, and the administration of EPA and DHA ethyl esters, by measuring their levels in plasma lipids. We also include the results of a previous study with different preparations of EPA and DHA, administered to similar groups of healthy individuals with an identical study design [6]. All treatments were carried out for a period of six weeks. Eight healthy subjects (four males and four females, aged 26-38 y) consumed 100 g/d of smoked salmon, which provided 383 mg of EPA and 544 mg of DHA. The amounts of EPA and DHA in the smoked salmon were measured through a quantitative analytical procedure. Two groups of eight subjects each (six males and two females) took one or three capsules of fish oil/day (Now Foods, Bloomingdale, IL), providing 150 mg EPA and 106 mg DHA or 450 mg EPA and 318 mg DHA as ethyl esters, respectively. Participants did not eat fish during the three weeks preceding the study. Blood was drawn at – 2, 0, 3, and 6 weeks (T_{-2}, T_0, T_3, T_6) of treatment in the morning in fasting conditions, using Li^+ heparin as the anticoagulant, and plasma was immediately prepared. Complete lipid analysis was carried out at each time point. Fatty acid data were expressed

as percentages of total fatty acids, as µg/mg total lipids, and as µg/ml plasma for each fatty acid. In the previous study [5], carried out with the same protocol, three (1 290 mg EPA and 960 mg DHA) or six (2 580 mg EPA and 1920 mg DHA) one-g capsules of a different type of preparation/day were given to two groups of eight healthy subjects. Measurements of fatty acid concentrations (µg/mg TL) allow to evaluate the absolute changes following treatments. There was no appreciable change in EPA and DHA levels between T_{-2} and T_0, and we are therefore reporting only the plasma increments between T_0 and T_6 for all four treatments: one capsule/day and fish, in this study, and three and six capsules/day in the previous study. Increments (µg/mg plasma total lipids) of both EPA and DHA are well correlated with the doses in the studies with capsules, with linear relationships that were expressed by equations with R^2 very close to 1.0. On the other side, it was not possible to define any kind of equation which would include also the data obtained with fish. The excellent relationships for increments *vs* doses are rather surprising considering that studies were carried out several years apart, although with an identical protocol *(table 1)*. It is also quite apparent that increments with the dose are much smaller for DHA than for EPA (slopes 0.002 *vs* 8.67, respectively). The most striking findings are that the increments of EPA and especially of DHA after fish intake are markedly much higher than with capsules. In fact, for EPA an increment of 8.8 µg/mg TL was obtained with an intake of 383 mg/day through fish ingestion *vs* an increment of 6.3 µg/mg TL (i.e. about 30% lower) after the intake of 450 mg/day (i.e. 17% higher) with a capsule. The difference between fish *vs* capsules is even greater in the case of DHA. With a daily dose of 544 mg DHA from fish, plasma increments were almost double than those obtained with 1 920 mg with capsules, that is a 3.5 fold higher dose. In order to obtain the same increments with a pharmaceutical preparation, assuming that linearity between intakes and plasma increments is retained, it would require 3 920 mg, corresponding to 12 capsules (320 mg DHA/capsule).

Table 1. *Net increments of plasma eicosapentaenoic (EPA) and docosahexaenoic (DHA) acids after supplementation of healthy volunteers with either fish or fish oil capsules (cps).*

	EPA	**DHA**
	Net increment µg/mg total lipids	
Fish (383 mg EPA + 544 mg DHA)	8.8 ± 1.2	8.5 ± 2.6
1 cps (150 mg EPA + 106 mg DHA)	2.8 ± 0.3	2.1 ± 0.7
3 cps (450 mg EPA + 318 mg DHA)	6.3 ± 1.3	3.2 ± 1.3
3 cps (1 290 mg EPA + 960 mg DHA)	13.2 ± 2.5	3.3 ± 1.3
6 cps (2 580 mg EPA + 1 920 mg DHA)	26.4 ± 3.3	4.8 ± 1.9

Data are means ± SD. For protocol details, including doses, please refer to the original papers.
Equations for the increments related to capsules intakes:
EPA, $y = 1.06 + 9.78 \times 10^{-3}$ R2 = 1.00 DHA, $y = 2.19 + 1.34 \times 10^{-3}$ R2 = 0.929

Discussion

The data obtained by comparing the increments in EPA and DHA levels in plasma lipids of a various groups of healthy subjects after administration as pharmaceutical preparations *vs* fish provide convincing evidence that the form of administration of small amounts of omega 3 fatty acids and, possibly, also their chemical features (triglyceride *vs* ethyl esters) affects the bioavailability of these compounds. The data were calculated as absolute increments in the amounts, as the conventional way of expressing fatty acid data, i.e. percentages, does not provide a correct overview of the FA status. In fac, by expressing the whole FA profile in terms of percentages, i.e. added up to a total of 100, one implies that increments of certain compounds are counterbalanced by compensatory reduction(s) of other FAs. Measurement of absolute amounts (μg/mg total lipids or /mL) and of their changes after administration provides quantitative information on relationship between intakes and levels in the circulation, i.e. on the bioavailability. The results therefore were expressed as changes in circulating levels in relation to intakes (amounts/day). Greater bioavailability of omega 3 fatty acids from fish than from pharmaceutical preparations is predictable as it is associated with a large mass of fats and thus administered in a very diluted form. Further, this route of intake is associated with a mass of tissue and fats that activate digestive processes, including those involved in lipid digestion and absorption. In addition, the mucosal surface involved in the absorption of a large mass is certainly greater than that involved in the absorption of a small volume. Capsules, conversely, provide just a small lipid bolus and, in the absence of a concomitant intake of other fats, the processes for lipid absorption may not be adequately activated. The results, quite beyond our prediction, may provide some clue as to why fish may be better than capsules in term of providing omega 3 fatty acids. Also, the observations that fish consumption, even at relatively low doses and few times/week, is highly protective toward cardiovascular diseases may find some grounds in our data.

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