British Journal of Nutrition (2007), **98**, 451–453
doi: 10.1017/S0007114507761779
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Invited Commentary

Dietary arachidonic acid: harmful, harmless or helpful?

Mammalian cells and tissues contain substantial amounts of the *n*-6 PUFA arachidonic acid, especially in their membrane phospholipids. For example, platelets from human adults living on a typical Western diet have about 25 % phospholipid fatty acids as arachidonic acid[1], while for human mononuclear cells, neutrophils, erythrocytes, skeletal muscle, cardiac tissue and liver phospholipids, arachidonic acid contents are about 22[2], 15[3], 17[1,4,5], 17[6], 9[4] and 20[5] % total fatty acids, respectively. This arachidonic acid can have two origins: the diet or endogenous synthesis from a precursor, particularly linoleic acid, which is consumed in fairly high amounts in most diets. Important dietary sources of preformed arachidonic acid are eggs and meat; fish also contain arachidonic acid. Typical intakes of arachidonic acid have been estimated to be between 50 and 300 mg/d for adults consuming Western-style diets[7–9]. The most well-recognised functional role of cell membrane arachidonic acid is as a cell signalling molecule, either in its own right or after its conversion to oxidised derivatives known as eicosanoids. The eicosanoid family of mediators includes prostaglandins, thromboxanes, leukotrienes, lipoxins and hydroxy- and hydroperoxy-eicosatetraenoic acids. To form eicosanoids, arachidonic acid is first released from cell membrane phospholipids by phospholipase enzymes. The free arachidonic acid then acts as a substrate for cyclooxygenase, lipoxygenase or cytochrome P450 enzymes, ultimately yielding the various eicosanoid metabolites. These metabolites have well-established roles in many pathological processes including thrombosis, inflammation and immunosuppression. Thus, drugs targeted at eicosanoid synthesis (aspirin, non-steroidal anti-inflammatory drugs, some steroids, cyclooxygenase-2 inhibitors) and actions (leukotriene receptor antagonists) have been developed and in some cases are widely used with good efficacy. The idea has developed that, since arachidonic acid-derived mediators are involved in so many pathologies, arachidonic acid itself must be harmful. This notion is compounded by observations that free arachidonic acid is a potent platelet aggregator, induces inflammatory responses and is an immunosuppressant. Finally, the many health benefits of long chain *n*-3 PUFA frequently involve an 'antagonism' of arachidonic acid: long chain *n*-3 PUFA partly replace arachidonic acid in cell membranes and inhibit arachidonic acid metabolism to eicosanoids. These observations have led to the idea that both arachidonic acid and its eicosanoid derivatives are harmful. This idea is supported by a study with arachidonic acid (6 g/d as an ethyl ester) in healthy human volunteers, which was stopped early (after 3 weeks) because of a dramatic increase in *ex vivo* platelet aggregation[10], which prompted concern about a potentially adverse pro-thrombotic action of dietary arachidonic acid.

An article in the current issue of the *British Journal of Nutrition* assesses the impact of increased dietary intake of arachidonic acid in an adult population with high fish intake[11]. This is the first study of arachidonic acid intake in such a population; previous studies in healthy adult human subjects have been conducted in low fish consumers in the USA[10,12–17] and in the UK[18–20]. In this new study, approximately 840 mg arachidonic acid/d was consumed by Japanese adults for 4 weeks. Habitual arachidonic acid intake was estimated to range between 110 and 270 mg/d with an average of about 175 mg/d. This is not unlike typical intakes reported for adults in Western countries[7–9,18]. Habitual intakes of EPA and DHA ranged from 42 to 691 and from 98 to 991 mg/d, respectively, with average intakes of about 310 and 550 mg/d respectively[11]. These are much greater than long chain *n*-3 PUFA intakes among those subjects involved in studies of arachidonic acid previously (e.g. 90 and 150 mg/d for EPA and DHA, respectively[18]). In this new study, the amount of arachidonic acid was increased in serum phospholipids (from 9·6 to 13·7 g/100 g total fatty acids) and TAG (from 1·4 to 2·3 g/100 g total fatty acids) with maximum incorporation occurring at 2 weeks of supplementation[11]. The increase in arachidonic acid content of serum phospholipids is consistent with that seen in plasma phospholipids in adults in the UK supplementing their diet with 680 mg arachidonic acid/d (from 9·3 to 15·9 g/100 g total fatty acids), in which maximum incorporation occurred at 4 weeks (an earlier time point was not examined)[18]. A washout period of 4 weeks resulted in a return of arachidonic acid in serum phospholipids and TAG to levels seen prior to starting supplementation[11]. Again, this is consistent with earlier observations for plasma phospholipids after a 4-week washout period[18]. In the study of Kusumoto *et al.* there was no effect of supplemental arachidonic acid on blood pressure, serum lipid and glucose concentrations or serum markers of liver function[11]. These findings are consistent with an earlier study conducted in the USA using 1·5 g arachidonic acid/d, which showed no effects on blood lipid or lipoprotein concentrations[14]. However, the main focus of this new study is platelet aggregation. Given this, it is unfortunate that the authors do not report the fatty acid composition of platelet phospholipids. Studies using data across populations with different patterns of PUFA intake have reported that platelet aggregation is highly related to the arachidonic acid and EPA contents of platelets[21]. In this new study, maximal aggregation of platelets in response to ADP, collagen or arachidonic acid and platelet sensitivity to ADP or collagen were not affected by dietary arachidonic acid supplementation[11]. Thus, the main conclusion from this new study is that increasing arachidonic acid intake by 840 mg/d does not

result in a pro-aggregatory state. One reason for this may be that the starting platelet content of arachidonic acid was already above that which results in a maximal aggregatory response. Additionally, the relatively high long-chain *n*-3 PUFA content expected to be present in these platelets may have prevented any pro-aggregatory effect of an increased arachidonic acid content from occurring. However, without seeing the data on platelet fatty acid composition in this study it is not possible to assess this further. Furthermore, no arachidonic acid-derived eicosanoids such as prostaglandin-I_2 and thromboxane-A_2 are reported here and so it is not possible to properly assess the functional impact of the supplement. As indicated earlier, an early study reported a marked increase in platelet aggregation after 6 g arachidonic acid/d for 3 weeks[10]. This was associated with increased arachidonic acid in platelets and increased urinary appearance of a prostaglandin-E metabolite. In another study, arachidonic acid (1·5 g/d for 7 weeks) only slightly increased platelet arachidonic acid (from 21 to 22·5 % of total fatty acids) and did not alter platelet aggregation in response to ADP, collagen or arachidonic acid, or prothrombin, partial thromboplastin or bleeding times[13]. The limited effect of 1·5 g arachidonic acid/d on platelet fatty acid composition probably accounts for the lack of a functional effect. Furthermore, this study suggests that platelet fatty acid composition in the study by Kusumoto *et al.*, which used 840 mg arachidonic acid/d, may have been little affected; this would account for the lack of functional effect on platelets. This strengthens the need to see the data for platelet fatty acid composition.

In contrast to what might be predicted[22–24], studies assessing a range of immune functions and inflammatory markers in healthy adults in response to increased intake of arachidonic acid (up to 1·5 g/d) have not identified any major effects[16–20]. Taken together with the studies on blood lipids, platelet reactivity and bleeding time[13,14], including this latest study[11], it seems appropriate to conclude that a significant increase in arachidonic acid intake by healthy adults, up to an intake of, say, 1·5 g/d appears unlikely to have any adverse effect. However, the earlier study by Seyberth *et al.*[10] suggests that higher intakes of arachidonic acid should be approached with caution. Furthermore, there is no information on the impact of increased arachidonic acid supply in disease. It is possible that inflammatory processes that already exist within an individual could be exacerbated by providing exogenous arachidonic acid. However, the discovery of novel anti-inflammatory mediators produced from arachidonic acid[25] and the identification of hitherto unknown anti-inflammatory actions of mediators previously considered to be pro-inflammatory in nature[26] indicate first, the complexity of this system and, second, that predicting the effect that increased arachidonic acid supply might have is difficult. Nevertheless, it is important to keep in mind that, just because there is little biological impact of an increase in arachidonic acid intake or status[11–20], there may still be significant benefit from a decrease in its intake or status.

It is important to note that a role for arachidonic acid in neurological development has been identified[27], that arachidonic acid-derived eicosanoids are not confined to pathology but have many physiological roles, that human breast milk contains arachidonic acid[28], that infant formulas, which include arachidonic acid (and DHA), are associated with improved growth and development[29,30] and that formula containing arachidonic acid (and DHA) has been shown to enable preterm infants to achieve immune development similar to that seen with breast-milk feeding[31] and to lower the risk of necrotising enterocolitis in preterm boys[32]. These observations suggest an important role for arachidonic acid in the normal growth and development of infants and demonstrate that harmful actions are not seen as a consequence to its provision, at least when given in combination with DHA.

In conclusion, this new study by Katsumoto *et al.* adds valuable new information to our knowledge about the impact of increased dietary intake of arachidonic acid[11]. Taken together with earlier studies[12–20], this study suggests that, rather than being harmful, moderately increased arachidonic acid intake is probably harmless in healthy adults, although the effect of intakes above 1·5 g/d are not known and the effect of increased intake in diseased individuals is not known. Furthermore, arachidonic acid appears to be an important constituent of infant formulas and in this setting may be helpful in growth, development and health.

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