Arachidonic Acid and Ischemic Heart Disease

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A number of studies have found a positive correlation between the amount of arachidonic acid (AA) in adipose tissue and the risk of ischemic heart disease (IHD). For example, Baylin and Campos (1) reported that AA in adipose tissue was correlated with the risk of nonfatal myocardial infarction (MI) in Costa Rica. Another study by Kark et al. (2) examined an Israeli population consuming a diet high in linoleic acid (LA) and reported a relation between risk of acute MI and adipose tissue AA but not that of LA. An earlier German report (3) showed a strong correlation between adipose AA and palmitic acid and angiographically documented coronary arteriosclerosis. On the other hand, a Norwegian case control study (4) found no increase in adipose tissue AA in patients with MI. In the study of Baylin and Campos (1), the amounts of AA in adipose tissue were 0.43 g/100 g fatty acids in controls and 0.47 g/100 g in patients, indicating that AA is still a minor fatty acid in this tissue. Nevertheless, the difference was clearly significant and could not be easily explained by a difference in dietary intake of AA. Importantly, the risk of MI cannot be correlated with a high AA level in other tissue lipids.

What are the possible explanations for such relations? In this paper, we emphasize that in the study of Baylin and Campos (1), the AA concentration in adipose tissue was positively correlated with the BMI, a well-known risk factor for MI. We argue that increased adipose tissue AA is related to the increased fatty acid transport in obesity, and its consequences for the partitioning of AA. Although an alternative explanation would be that the inflammatory stress linked to increased risk of MI is associated with a redistribution of AA due to phospholipase A2 activation, we do not find support for this hypothesis.

General features of AA partitioning into tissue lipids

AA has distinct physiologic roles as a membrane constituent, as precursor of eicosanoids, and as a regulator of gene expression via the peroxisome proliferator-activated receptor γ (PPARγ). Among all fatty acids, it is most preferentially incorporated into glycerophospholipids. As a consequence, less AA is partitioned to triglycerides (TGs) including the adipose tissue TGs, and to oxidation (5). The basis for the phospholipid (PL) preference is the fatty acid specificities of the enzymes catalyzing reacylation of lyso-PL and transacylation reactions [for references see (6–8)]. For example, lysophosphatidylcholine (PC) acylCoA acyltransferase has a distinct preference for AA, and transacylations favor retention of AA in phosphatidylethanolamine with time. The retention of AA in PLs is extremely efficient when the supply of PUFAs is short, as in essential fatty acid (EFA) deficiency (9). However, the selective acylation into PLs has a limited capacity. With increasing access of PUFAs and/or oleic acid that compete with AA for this acylation, more AA is incorporated into cellular TGs and/or recirculated in VLDL to the adipose tissue (10). Therefore, there are 2 fundamental aspects of fatty acid transport: one is the optimal storage, mobilization, and utilization of fatty acids as a fuel; the other is the buildup of the PUFA and eicosanoid precursor pools in all tissues. The 2 are partially overlapping. Notably, when the specific pathways for retention of PUFAs in PLs become saturated, the excess PUFAs, including AA, enter the pathways designed for fuel transport. Due to competition between PUFAs for acylation into PLs, a high intake of LA, even though this fatty acid is the precursor of AA, may decrease the AA level in PLs and increase AA in TGs.

There are also other mechanisms that tend to minimize AA accumulation in adipose tissue TGs. AA ester bonds of chylomicron and VLDL TGs are relatively resistant to lipoprotein lipase (LPL) (11), and AA is preferentially mobilized from adipose tissue via hormone-sensitive lipase (12). A significant transport of AA from liver to other tissues occurs as 2-AA-lyso-PC, and much AA is formed in extrahepatic tissues from LA taken up as FFAs (6). Although AA in the FFA fraction is low, the turnover is rapid, and the daily turnover in humans may amount to 1.1–2.1 g (6). The body thus acquires its tissue AA pools by multiple pathways under strict control of PL acylation and of the potentially harmful release of AA as FFAs into blood. The formation of AA from LA is regulated both via phospholipase A2 activation, we do not find support for this hypothesis.

Relation between BMI and adipose tissue AA

The AA level increases with BMI in adipose tissue, but decreases in RBC PLs in obese individuals (1). PL-AA in
muscle correlates inversely with insulin resistance (13), and obese humans have lower concentrations of AA in serum PLs compared with nonobese individuals (14). With initiation of dieting, the AA in PLs of obese patients normalizes and remains increased during rapid weight loss, but declines again when weight loss stops (14). In addition, increased AA amounts in adipose tissue were reported in obese children (15). A seemingly puzzling feature is that in adults, although AA in plasma PLs decreases in obesity, other Δ-6 desaturase products, i.e., γ-linolenic acid [18:3(n-6)] and dihomo-γ-linolenic acid [20:3(n-6)], increase (14), whereas in obese children, all 3 Δ-6 desaturase products increase (16). We contend that all of these findings can be explained by the following “PUFA flow model”: the increased fatty acid traffic in obese individuals (17) causes a competition between unsaturated fatty acids for acylation into the 2-position of PL. The increased flux of LA in obesity may increase not only acylation of LA into PLs and TGs but also the metabolism of LA-CoA by Δ-6 desaturase, analogous to what was observed in fasting guinea pigs (18). It may thus be associated with an increased formation of AA and other Δ-6 desaturase products, but the net effects on PL fatty acid composition will vary with the balance between desaturase action and PL acylation, and thereby differ between adults and adolescents. This model would also explain why the study of Kark et al. (2), which emphasizes the high LA content in the Israeli diet, reported the highest and least variable values for both LA and AA in adipose tissue. The lack of correlation with adipose tissue AA in the Norwegian study (4) can be linked to a lower and more variable adipose tissue AA level and lower LA levels, probably due to a more variable dietary LA intake in the studied population.

When comparing the relatively rapid changes in plasma PL and TG AA levels with adipose tissue fatty acid composition, one must bear in mind that the half-life of adipose tissue in humans in energy balance is ~600 d (19). The fatty acid composition of adipose tissue therefore reflects the dietary fat intake and other features of the metabolic situation during the previous 2–3 y (20). This may explain why Nelson et al. (21), after dietary treatment of human volunteers with 1.7 g AA/d for 50 d, did not observe any increase in adipose tissue AA despite a significant increase of AA in plasma PLs and TGs. An increase in the AA level of adipose tissue with BMI may be explained by increased fatty acid flux and saturation of the selective pathways for AA retention in PLs only if this occurs over a long time. A constant mass of adipose tissue may vary in turnover rate, e.g., due to variations in the degree of physical activity and total energy consumption. If AA is preferentially mobilized from adipose tissue (12), one would expect that a high turnover rate even with an unchanged net mass would decrease the AA in adipose tissue. A sedentary lifestyle with a low rate of fatty acid oxidation and high VLDL production will cause a continuously increased competition between AA and other fatty acids for PL acylation and increased recycling of fatty acids, including AA, in VLDL. Downregulation of LPL in muscles but not in adipose tissue is expected to further favor AA retention in adipose tissue in sedentary people. Direct experimental support for this hypothesis is lacking in humans, however, and data from rats, a high-AA species, do not reveal a decrease in adipose tissue AA after exposure to physical exercise (22).

The data on obese children (15,16) indicate that high AA in adipose tissue may be established early in life. There is evidence for a role of (n-6) fatty acids in growth regulation and adipogenesis at an early age. The strong retardation of growth and poor development of adipose tissue in EFA-deficient animals are well known. In preterm infants, low (n-6) fatty acid values are associated with reduced growth (23). A high LA diet given to dams (rats) is linked to hyperplastic adipose tissue in suckling pups at d 17 (24). These findings may be related to the observation that AA may have a specific role in adipogenesis by promoting differentiation of preadipocytes into mature fat cells via PPARγ receptor-mediated action (25). It is thus possible that one group of individuals may establish a high AA level in adipose tissue early in life and that this is related to adult obesity and the risk of MI.

**AA in adipose tissue, plasma FFA, and risk for myocardial infarction**

Because fatty acids are mobilized from adipose tissue as FFAs, an increased proportion of AA in the mobilized FFAs might influence platelet, white blood cell, or endothelial function by stimulating eicosanoid formation and increase the cardiac risk. However, the Norwegian case control study (26) of patients with MI showed no increase in the proportion of AA in plasma FFAs, which was 0.87 and 0.86 g/100 g in the patient and control groups, respectively. The proportion was higher than in adipose tissue in both groups (0.26 vs. 0.25 g/100 g) (4). Notably, there was no correlation between adipose tissue AA and AA in the FFA fraction during fasting (27). Available human data show that the fractional turnover rate for AA is faster than for other FFAs (28). AA should thus not be enriched in the FFA pool during its metabolism. Yet, an increased AA in adipose tissue in combination with the increase in total FFAs may raise plasma FFA-AA in obese and/or insulin-resistant individuals without increasing the proportion of AA in FFAs. However, data on plasma FFA-AA in obesity and insulin resistance are lacking. In conclusion, there is therefore no support for the idea that increased adipose tissue AA is linked to an increase in plasma FFA-AA of such a magnitude that it could influence endothelial, platelet, or white blood cell function by a direct effect on eicosanoid formation.

The AA that is released by phospholipase A2 in inflamed tissues and not metabolized to eicosanoids is reacylated into PL, oxidized, or released into blood and bound to albumin. The origin of the AA in the FFA fraction in plasma is not well understood. Tissue sources other than the normally predominant FFA sources, i.e., the action of LPL on lipoprotein TGs and of hormone-sensitive lipase on adipose tissue, may be important. We therefore asked whether inflammatory stress elsewhere in the body could increase partitioning of AA to adipose tissue. A number of findings argue against this possibility. First, the Norwegian data (26,27) on MI patients do not indicate an increased AA release as FFAs due to arteriosclerosis or endothelial damage. Second, adipose tissue AA was low in both adult (29) and pediatric (30) patients with Crohn’s disease and in patients with rheumatoid arthritis (31). Third, studies in polymorphonuclear leukocytes (32) could not link a large increase of AA in TGs to increased free AA or eicosanoid formation. Another issue is whether inflammatory activity within the adipose tissue itself might increase the AA level. Production by adipose tissue of several adipokines involved in inflammation is increased in obesity, which is characterized by a state of chronic low-grade inflammation. This may be linked causally to insulin resistance and the metabolic syndrome. According to one view, the increased production of inflammatory cytokines and acute phase proteins by adipose tissue in obesity relates primarily to localized events within the expanding fat depots (33). However, according to Fain et al. (34) the enhanced total release of tumor necrosis factor-α,
IL-8, and IL-10 by adipose tissue in severely obese individuals was due to nonfat cells. Whether the inflammatory state of obesity is linked to increased AA release and recirculation is unknown. Currently, there is thus no clear evidence that chronic inflammation is linked to increased AA in adipose tissue.

In conclusion, the relation between IHD and the amount of AA in adipose tissue, examined in 3 studies (1–3), cannot yet be interpreted in terms of cause and effect. AA in adipose tissue cannot be considered an independent risk factor. The increase with BMI, which is in turn related to risk of MI, may be explained on the basis of known features of AA transport, preferential acylation, and formation. Increased competition between AA and LA for acylation into PLs and increased production of Δ-6 desaturase products secondary to increased flux of LA as FFA are key factors. In our view, this PUFA flow model may also explain why the correlation is seen in populations with a high LA intake (1,2) but not in others (4). Additional mechanisms may contribute to the increase of AA in adipose tissue early in life in obese children. Evidence for a link between systemic inflammation and increased adipose tissue AA secondary to increased AA release by phospholipase A2 is lacking. Finally, it is worth emphasizing that many of the enzymes involved in the selective retention of AA in PLs have not been purified or cloned. This is necessary to understand all aspects of changes in AA distribution and its consequences.

### LITERATURE CITED