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ABSTRACT

Background Leukotrienes are inflammatory mediators generated from arachidonic acid (polyunsaturated n-6 fatty acid) by the enzyme 5-lipoxygenase. Since atherosclerosis involves arterial inflammation, we hypothesized that a polymorphism in the 5-lipoxygenase gene promoter could relate to atherosclerosis in humans and that this effect could interact with the dietary intake of competing 5-lipoxygenase substrates.

Methods We determined 5-lipoxygenase genotypes, carotid-artery intima-media thickness, and markers of inflammation in a randomly sampled cohort of 470 healthy, middle-aged women and men from the Los Angeles Atherosclerosis Study. Dietary arachidonic acid and marine n-3 fatty acids (including a competing 5-lipoxygenase substrate that reduces the production of inflammatory leukotrienes) were measured with the use of six 24-hour recalls of food intake.

Results Variant 5-lipoxygenase genotypes (lacking the common allele) were found in 6.0 percent of the cohort. Mean (±SE) intima-media thickness adjusted for age, sex, height, and racial or ethnic group was increased by 80±19 μm (95 percent confidence interval, 43 to 116; $P<0.001$) among carriers of two variant alleles, as compared with carriers of the common (wild-type) allele. In multivariate analysis, the increase in intima-media thickness among carriers of two variant alleles (62 μm, $P<0.001$) was similar in this cohort to that associated with diabetes (64 μm, $P=0.01$), the strongest common cardiovascular risk factor. Increased dietary arachidonic acid significantly enhanced the apparent atherogenic effect of genotype, whereas increased dietary intake of n-3 fatty acids blunted the effect. Finally, the plasma level of C-reactive protein, a marker of inflammation, was increased by a factor of 2 among carriers of two variant alleles as compared with that among carriers of the common allele.

Conclusions Variant 5-lipoxygenase genotypes identify a subpopulation with increased atherosclerosis. The observed diet-gene interactions further suggest that dietary n-6 polyunsaturated fatty acids promote, whereas marine n-3 fatty acids inhibit, leukotriene-mediated inflammation that leads to atherosclerosis in this subpopulation.

Source Information

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