Novel action of n-3 polyunsaturated fatty acids: inhibition of arachidonic acid-induced increase in tumor necrosis factor receptor expression on neutrophils and a role for proteases.

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OBJECTIVE: Neutrophils and tumor necrosis factor (TNF) play important roles in the pathogenesis of rheumatoid arthritis (RA). Modulation of TNF receptors (TNFRs) may contribute to the regulation of tissue damage, and n-6 polyunsaturated fatty acids (PUFAs) such as arachidonic acid (AA) can increase the expression of TNFRI and TNFRII on neutrophils. Because the n-3 PUFAs are antiinflammatory in RA, we examined whether, as a novel mechanism of action, n-3 PUFAs can antagonize the AA-induced increase in TNFR expression. METHODS: Human neutrophils were treated with PUFAs and examined for changes in surface expression of TNFRs by flow cytometry. Translocation of protein kinase C (PKC) and activation of ERK-1/2 MAPK were determined by Western blotting. Intracellular calcium mobilization was measured in Fura 2-loaded cells by luminescence spectrometry. RESULTS: Pretreatment of neutrophils with nanomolar levels of n-3 PUFAs, eicosapentaenoic acid, or docosahexaenoic acid led to a marked inhibition of the AA-induced up-regulation of TNFRs I and II. Such pretreatment, however, did not prevent AA from stimulating the activities of PKC and ERK-1/2, which is required for the actions of AA or its ability to mobilize Ca(2+). Nevertheless, treatment with n-3 PUFAs caused the stimulation of serine proteases that could cleave the TNFRs. CONCLUSION: These findings suggest a mechanism by which the n-3 PUFAs inhibit the inflammatory response in RA, by regulating the ability of AA to increase TNFR expression. These results help fill the gaps in our knowledge regarding the mechanisms of action of n-3 PUFAs, thus allowing us to make specific recommendations for the use of n-3 PUFAs in the regulation of inflammatory diseases.