Sex modulation of pro-inflammatory lipid mediator biosynthesis during acute inflammation

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Leukotrienes (LTs) and prostaglandins (PGs) are lipid mediators produced from arachidonic acid (AA) that are involved in several inflammatory disorders characterized by a sex bias (i.e. asthma, rheumatoid arthritis, gout). Here, we report about a sex bias in the biosynthesis of LTs and PGs. Starting from *in vitro* sex differences in LT biosynthesis in human neutrophils and monocytes due to suppression by androgens, we have investigated the role of sex in LT biosynthesis in zymosan-induced peritonitis in mice, a model of acute inflammation, where LTs play pivotal roles in the pathophysiology. Upon zymosan injection, higher vascular permeability and cell influx in the peritoneal cavity was evident for female mice, accompanied by significantly higher LT levels in the peritoneal exudates. Interestingly, orchidectomy of male mice increased the levels of LTs in the exudates compared to sham-treated animals. On the cellular level (resident peritoneal macrophages), these sex differences can be explained by disparities in the subcellular localization of 5-lipoxygenase (5-LO) with lower LT production in male cells. Intriguingly, opposite sex differences were observed for PG biosynthesis in zymosan-induced peritonitis, with higher PG formation in males. While no sex differences in PG levels were observed in the early phase (< 4 hrs), higher production of PGE_2 was evident in exudates of male mice in the late phase of the inflammatory response (4 - 8 hrs), seemingly due to PG production by infiltrating neutrophils, as confirmed by elevated myeloperoxidase levels. Note that these sex differences in LT and PG biosynthesis were obvious also in carrageenan-induced pleurisy in rats. Thus, after intrapleural carrageenan injection, higher levels of PGE_2 were found in pleural exudates of male rats (6 - 8 hrs), where inflammation is sustained by neutrophils. In agreement with these findings, isolated neutrophils from human blood of males synthesized higher amounts of PGE_2 upon ionophore stimulation as compared to neutrophils from female blood. Of interest, blockade of LT synthesis in isolated neutrophils as well as in zymosan-induced mouse peritonitis by MK886 abolished the sex differences in PGE_2 synthesis, suggesting that elevated PGE_2 synthesis in males might be due to lower LT formation. Conclusively, our data clearly demonstrate that sex is an important variable in the biosynthesis of pro-inflammatory eicosanoids with consequences for the inflammatory response.