Sex differences in prostaglandin biosynthesis in neutrophils

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Here we show that the inflammatory reaction sustained by prostaglandin (PG) release from neutrophils is stronger in males compared to females. PG are key mediators in several inflammatory disorders that are characterized by a sex bias. We measured PGE_2 levels in peritoneal exudates of male and female mice after zymosan injection, starting from 15 minutes until 4 hours. 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. Intriguingly, the same sex differences in PG biosynthesis were observed 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 infiltrated 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 leukotriene (LT) synthesis in isolated neutrophils by MK886 abolished the sex difference in PGE_2 synthesis, suggesting that elevated PGE_2 production in males might be due to lower LT formation. In fact, in neutrophils, ionophore stimulation rapidly activates 5-lipoxygenase leading to a sex-biased product formation (i.e. leukotriene B_4 (LTB_4) higher in female cells [Pergola C. et al., 2008]. No sex differences were found in the expression of cyclooxygenases as well as in the release of arachidonic acid upon ionophore stimulation. Of note, these sex differences in LT biosynthesis as well as the effect of MK886 were present also in carrageenan-induced pleurisy in rats. Conclusively, our data reveal that sex is an important variable in the biosynthesis of pro-inflammatory leukotrienes as well as prostaglandins with consequences for the inflammatory response.
Pergola C. et al, (2008).*PNAS.*105:19881-19886