REGULATION OF PROSTAGLANDIN BIOSYNTHESIS BY INDUCIBLE NITRIC-OXIDE SYNTHASE IN KNOCKOUT MICE

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In the present study, by comparing the responses in wild-type mice (WT) and mice lacking (KO) the inducible (or type 2) nitric oxide synthase (iNOS), we investigated the correlation between endogenous nitric oxide (NO) and prostaglandin (PGs) generation *in vivo* (carrageenan-induced pleurisy) and *ex vivo* (peritoneal macrophages).
The inflammatory response in iNOSKO mice was significantly reduced in respect to WT animals, as demonstrated by the exudate volume (-63%) and the number of infiltrated cells (-62%). The levels of NOx in the pleural exudate from carrageenan-treated mice were significantly ($p<0.01$) decreased in iNOSKO mice (16 ± 7.6 nmoles/mice) compared to WT animals (133 ± 9 nmoles/mice). Similarly, the amounts of PGE_2 in the pleural exudate of carrageenan-treated animals were significantly ($p<0.01$) lower in iNOSKO compared to WT mice (120 ± 20 pg/mice *vs* 308 ± 51 pg/mice). Also the amounts of 6-keto-$PGF_{1\alpha}$ produced by lungs from carrageenan-treated iNOSKO mice (1.01 ± 0.10 ng/tissue mg) were significantly ($p<0.01$) reduced compared to WT carrageenan-treated mice (2.1 ± 0.09 ng/tissue mg).
Peritoneal macrophages were obtained from WT animals and iNOSKO mice, and PGE_2 was quantified after stimulation with lipopolysaccharide (10γ/ml) and γ-interferon (100U/ml) for 24 h to induced COX-2. Total NOx production was completely abolished in cells from iNOSKO mice compared to cells from WT animals. PGE_2 formation by cells from iNOSKO mice was decreased (-90 %) compared to cells from WT animals (4.94 ± 0.49 ng/10^6 cells *vs* 56.5 ± 1.86 ng/10^6 cells, $p<0.001$).
In conclusion our results confirms, by the use of iNOSKO mice, that NO positively modulates PG biosynthesis *in vivo* and *ex vivo*. Thus NO seems to modulate the inflammatory response also through COX pathway amplification.