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


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 PGE₂ 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-PGF₁α 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 PGE₂ 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. PGE₂ formation by cells from iNOSKO mice was decreased (-90 %) compared to cells from WT animals (4.94 ± 0.49 ng/10⁶ cells vs 56.5 ± 1.86 ng/10⁶ 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.

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