ABSENCE OF FUNCTIONAL PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR-ALPHA (PPAR-α) RECEPTOR INHIBITS THE ANTI-INFLAMMATORY EFFECT OF GLUCOCORTICOIDS

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The glucocorticoid receptor (GR) and peroxisome proliferator-activated receptor-α (PPAR-α) play important roles in both physiological and pathological conditions involving cell growth and differentiation, lipolysis, control of glucose metabolism, immunity and inflammation. In fact, recent studies suggest that endogenous of PPAR-α ligands, like fatty acids, may also have anti-inflammatory properties, even if the molecular mechanisms responsible for these activities have not yet been completely clarified. The present study was designed to gain a better understanding of the possible cross talk between GR and of PPAR-a in a model of lung inflammation (carrageenan-induced pleurisy). In particular, we have investigated if the genetic depletion of PPAR-α receptor (PPAR-α knock out mice) is able to attenuate the well-known anti-inflammatory effect of dexamethasone (DEX, a synthetic glucocorticoid). We show that the anti-inflammatory activity exhibited by DEX observed in PPAR-α wild-type (WT) mice is impaired in the PPAR-α knock out mice. Moreover, in PPAR-α knock out mice we have observed a significant inhibition of the ability of DEX to reduce: (i) the degree of lung injury, (ii) the rise in myeloperoxidase (MPO) activity, (iii) the increase of poly(ADP-ribose) polymerase (PARP) activity, tumour necrosis factor alpha (TNF-α and interleukin (IL)-1β levels, (iv) inducible nitric oxide synthase (iNOS), (v) lipid peroxidation, vi) nitrotyrosine formation, vii) cyclo-oxygenase (COX-2) expression, (viii) the IκB-α degradation, caused by carrageenan administration.
In conclusion these results suggest that the in vivo anti-inflammatory property of DEX is also related to the functional presence of PPAR-α receptor.