ESTROGEN RECEPTOR ANTAGONIST ICI 182,780 INHIBITS THE ANTI-INFLAMMATORY EFFECT OF GLUCOCORTICOIDS

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The glucocorticoid receptor (GR) and estrogen receptors (ER) 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 17β-estradiol, like glucocorticoids, 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 ER in a model of lung inflammation (carrageenan-induced pleurisy). In particular, we have investigated if ICI 182,780, a selective ER-α antagonist, is able to attenuate the well-known anti-inflammatory effect of dexamethasone (DEX, a synthetic glucocorticoid) in ovariectomized rats. We show that ICI 182,780, a selective ER-α antagonist, reverses the anti-inflammatory activity exhibited by DEX. Moreover, the co-administration of ICI 182,780 significantly inhibited 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 addition, quantitative PCR shows that DEX down-regulates GR and up-regulates GILZ levels, whereas ICI 182,780 doesn't counteract these effect. In conclusion these results suggest that the in vivo anti-inflammatory property of DEX is also related to the ER-α.