ESTROGEN RECEPTOR-ALPHA IS INVOLVED IN THE REGULATION OF GLUCOSE HOMEOSTASIS AND THE VASCULAR RESPONSE TO INFLAMMATORY CYTOKINES IN MICE

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The ovarian estrogen 17ß-estradiol acts predominantly via two distinct nuclear estrogen receptor isoforms, ERα and ERß. They are expressed in a tissue-specific way and mediate distinct biological activities. Both ER isoforms appear to mediate anti-inflammatory effects in a variety of tissues including the vascular wall. By using selective and nonselective ER agonists in wild-type (wt) and ER-knock out (-/-) mice, we have investigated in this study the relative contribution of each ER isoform to the progression of streptozotocin (STZ)-induced diabetes *in vivo* and the potential protection of the vascular wall from inflammatory cytokines *ex vivo*. Diabetes was induced in 8-week-old mice by a single i.p. injection of 150 mg/Kg STZ. The cumulative incidence of diabetes over 3 weeks after STZ injection was similar in wt and mutant mice. Exposure to STZ, however, caused significantly greater mortality in ERß-/- (32%) than in ERα-/- (16%) or wt (15%) mice. Plasma glucose levels were higher in both ERα-/- (454±26 mg/dl, n=22) and ERß-/- (446±29 mg/dl, n=19) mutant mice as compared with wt mice (382±17 mg/dl, n=47), suggesting that both ER subtypes are involved in the regulation of glycaemic control in settings of insulin deficiency. In view of the more severe phenotype of STZ-diabetes in ERß-/- mice, vascular biology studies were performed in the aorta isolated from wt and ERα-/- mice. Cultured aortic rings were stimulated with a cytokine mixture comprising TNF-α, interleukin-1ß and interferon-γ for 24 h in the presence or absence of test compounds. Treatment with 1 nM estradiol reduced by 30% the functional expression of inducible NO synthase (iNOS) as assessed by immunoblotting analysis in cultured rat aortic rings isolated from both normoglycaemic and STZ-diabetic wt mice. Application of the selective ERα agonist propyl pyrazole triol (PPT, 1 μM) reproduced this action of estradiol, whereas the selective ERß agonist diarylpropionitrile (DPN, 1 μM) tended to enhance iNOS formation in aortic rings from both groups of animals. The negative regulation of aortic iNOS by estradiol was abrogated in ERα-/- mice but could still be detected in ERß-/- mice. To sum up, both ER isoforms are involved in the regulation of glycaemic control after STZ injection in mice whereas ERß appears to confer greater protection than ERα against insulin-deficient diabetes progression and severity. By contrast, ERα activation confers protection to the vascular wall of both normoglycaemic and STZ-diabetic mice by preventing excess iNOS-driven NO production in response to proinflammatory cytokines.