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, ER\(\alpha\) and ER\(\beta\). 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 \(\textit{in vivo}\) and the potential protection of the vascular wall from inflammatory cytokines \(\textit{ex vivo}\). 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 ER\(\beta\)-/- (32%) than in ER\(\alpha\)-/- (16%) or wt (15%) mice. Plasma glucose levels were higher in both ER\(\alpha\)-/- (454±26 mg/dl, n=22) and ER\(\beta\)-/- (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 ER\(\beta\)-/- mice, vascular biology studies were performed in the aorta isolated from wt and ER\(\alpha\)-/- mice. Cultured aortic rings were stimulated with a cytokine mixture comprising TNF-\(\alpha\), interleukin-1\(\beta\) and interferon-\(\gamma\) 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 ER\(\alpha\) agonist propyl pyrazole triol (PPT, 1 \(\mu\)M) reproduced this action of estradiol, whereas the selective ER\(\beta\) agonist diarylpropi nitrile (DPN, 1 \(\mu\)M) tended to enhance iNOS formation in aortic rings from both groups of animals. The negative regulation of aortic iNOS by estradiol was abrogated in ER\(\alpha\)-/- mice but could still be detected in ER\(\beta\)-/- mice. To sum up, both ER isoforms are involved in the regulation of glycaemic control after STZ injection in mice whereas ER\(\beta\) appears to confer greater protection than ER\(\alpha\) against insulin-deficient diabetes progression and severity. By contrast, ER\(\alpha\) 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.