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# 硕 士 学 位 论 文

# IGF1R在雌激素保护胰岛功能和存活中的作用及其机制研究

# Role and mechanism of IGF1R in estrogen protection of pancreatic β-cell-function and survival

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# 摘　要

雌激素（E2），能够直接作用于胰岛β细胞，促进胰岛素分泌并防止多种因素引起的β细胞凋亡，对胰岛β细胞的存活和功能具有重要保护作用，因而可能在糖尿病的治疗和预防中发挥重要作用。但目前人们对E2的胰岛保护机制并不十分清楚。与E2相似，胰岛素生长因子（IGF1）对胰岛β细胞的功能与存活也具有保护作用，并且其受体IGF1R与雌激素受体（ER）(主要是ERa）在神经、血管、乳腺、子宫等多种组织中均有重要相互作用。因此我们推测IGF1R可能在E2的胰岛保护中发挥重要作用。

目的 探索IGF1R在E2胰岛β细胞保护中的作用，以明确E2的胰岛保护作用机制，为其可能的临床应用提供依据。

材料与方法 利用体外培养的胰岛β细胞系Min6细胞，以1%氧诱导缺氧损伤模型，用CCK8 检测细胞增殖，jc-1试剂检测线粒体膜电位，Tunel检测细胞凋亡，通过Western Blot检测相关蛋白的变化，并计划通过繁育胰岛β细胞特异性敲除IGF1R基因小鼠，在体内观察其在E2对胰岛保护中的作用。

结果 在缺氧条件下，E2促进Min6细胞增殖，减少细胞凋亡，此作用在加入IGF1R的抑制剂JB-1后消失。E2可以快速激活Akt以及ERK的磷酸化。 此作用在阻断IGF1R后消失。E2对胰岛β细胞保护作用在应用PI3K抑制剂LY294002、ERK通路抑制剂PD58059后消失。1%氧降低了线粒体膜电位，E2缓解线粒体膜电位损伤，这一作用在加入IGF1R 的抑制剂JB-1后消失。

结论 缺氧条件下，E2对胰岛β细胞存活具有显著保护作用，IGF1R及其下游两个关键信号通路PI3K/Akt、ERK介导了E2的胰岛β细胞保护作用。

关键词 糖尿病；胰岛素样生长因子1受体；雌激素；胰岛；缺氧

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# Abstract


Estrogen (E2) can act directly on the islet beta cells to promote insulin secretion and prevent beta cell apoptosis caused by many factors, thus plays an important pro-tective effect on islet beta cell survival and function, and may be of great significance in the treatment and prevention of diabetes. But at the moment, the mechanisms of E2 proteciton of islet function and survival remains unclear. Similar to E2, insulin growth factor (IGF1) also plays a protective role in islet beta cell function and survival, and a close interaction of its receptor (IGF1R) and estrogen receptor (ER, mainly ERa) was frequently reported in nerve, blood vessel, breast, uterine and other organizations.

OBJECTIVE—To explore the role of IGF1R in E2 protection of pancreatic beta cell function and survival.

RESEARCH DESIGN AND METHODS—Using pancreatic beta cell line Min6 cells, we investigated the E2 actions in beta cell survival under hypoxic condition. One percent oxygen was adopted to induce hypoxic damage, CCK8 was used to detect cell proliferation, jc-1 reagents was used to detect mitochondrial membrane potential, and Tunel was used to detect apoptosis. Protein expression and phosphory-laton was measured by Western Blot. Pancreatic beta cell specific IGF1R knockout mouse model was generated by cre-loxp strategy.

RESULTS—Under the condition of hypoxia, E2 increased Min6 cell proliferation, reduced the apoptosis, which was blocked by IGF1R inhibitors JB-1. E2 quickly acti-vated phosphorylation of Akt and ERK, which was abolished by IGF1R inhibition. The protective effects of E2 on pancreatic beta cell survival disappeared in the pres-ence of PI3K inhibitor LY294002, and ERK inhibitor

PD58059. E2 ameliorated hy-poxia- induced damage of mitochondrial membrane potential, which was blocked by IGF1R inhibitor JB–1.

Conclusion—E2 plays important protective roles in pancreatic beta cell survival under hypoxic condition, in which IGF1R and its two key downstream signaling pathway-PI3K and ERK exert indispensable roles.

Key Words—diabetes; Insulin-like growth factor 1 receptor; Estrogen; pancreatic beta cell; Hypoxia

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