Progesterone-Induced Apoptosis in Insulin-Secreting Cells: Insights into the Understanding of Gestational Diabetes Pathogenesis

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Introduction: During pregnancy, the inability of the pancreatic islets to ensure the increased insulin demand can result in gestational diabetes (GD). High plasma progesterone concentrations overlap with GD onset and may therefore contribute to the impaired insulin secretion and increased peripheral insulin resistance. Estrogens, on the other hand, have been associated to an antidiabetic function. In this study we examined the effects of progesterone and estriol on death of insulin-producing RINm5F cells. Also, we analyzed the involvement of progesterone in the oxidative stress and unfolded protein response (UPR), an event that can trigger cell death if endoplasmic reticulum (ER) dysfunction is severe or prolonged.

Material and Methods: RINm5F cells were incubated with progesterone (0 to 100 µM), in the presence or absence of α-tocopherol (40 µM), and/or estriol (25 µM) for 24 or 48h. The lost of cell membrane integrity and DNA fragmentation were analyzed by flow cytometry. Apoptosis occurrence was confirmed by detection of caspase activation. Expression of the proteins involved in UPR such as CREB-2 and CHOP was evaluated by western blotting. Results and Discussion: Progesterone induced apoptotic cell death, confirmed by caspase activity detection, which was attenuated by pre-incubation of cells with α-tocopherol. The pre-incubation with estriol resulted in an increase of the number of apoptotic cells, though this estrogen per se had only little effect. Progesterone also increased the expression of the proteins CREB-2 and CHOP in a time and concentration dependent manner. Conclusions: Progesterone may contribute to GD development, through a direct toxic effect to insulin-producing cells, which depends on oxidative stress. Also, the differential expression of UPR-related proteins following exposure to progesterone indicates that ER stress can lead to an accumulation of unfolded/misfolded proteins that may contribute to the observed effects.

Key Words: Progesterone, estrogens, β-cell, apoptosis, oxidative stress
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