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Expression of p53 and bcl2 as indicator of cell damage in human vascular model with high levels of glucose

U Medina-Moreno[1,2], M Pierdant Perez[1], F Valadez Castillo[1], P Mandeville[1], JA Gonzalez-Correa[3], A Gordillo-Moscoso[1]. *[1]Universidad Autónoma de San Luis Potosí, Facultad de Medicina, Epidemiology 78210, Mexico, [2]Universidad Complutense de Madrid, Facultad de Medicina, Pharmacology 28040, Spain, [3]Universidad de Malaga, Facultad de Medicina, Pharmacology 29071, Spain*

Background: Vascular smooth muscle cells (VSMC) cultured in chronic hyperglycemic conditions increase the production of reactive oxygen species (ROS), generating oxidative stress, alterations in apoptosis, and in a minor degree, proliferation alterations. Oxidative stress induces the expression of p53, a protein regulated by several members of the Bcl2 family, which modifies the mitochondrial permeability and triggers pro-apoptotic factors. This process alters the vascular lumen and could partially explain the diabetic's microvascular damage. It is still unknown if these alterations could be induced by a direct genotoxic effect of hyperglycemia in itself.

Objective: Evaluation of the effect of several different concentrations of D-glucose in clinical ranges (5.50 mmol/L, 10.00 mmol/L, 16.66 mmol/L and 27.77 mmol/L) over cultured VSMC obtained from human aorta and the expression of p53 and Bcl2 at 48 hours, 3 and 6 weeks of exposure.

Materials and methods: VSMC cultures were obtained by explant from aorta fragments derived from cadaveric donors (1hr postmortem). The cells were characterized by immune-staining and confocal microscopy. The study design was an experimental essay randomized by time blocks, where cell growth was evaluated by counting and the level of expression of p53 and BCL2 by final point polymerase chain reaction (PCR).

Results: There was no statistical difference in the cell growth factor. An interaction effect was noted between treatment and time for cell growth, as well as for the expression of both proteins ($p< 0.001$ for p53 and 0.013 for Bcl2). This observation was noticed because of the low protein expression between D-glucose levels of 27.77 mmol/L and control culture conditions (5.50 mmol/L) at 48 hours ($p= 0.0249$ for p53 and 0.016 for Bcl2), effect that was inverted at 6 weeks for p53 between the control group and the 16.66 and 27.77 mmol/L groups ($p= 0.0241$ and 0.0473, respectively); as well as for the control group and the 27.77 mmol/L group ($p=0.0109$) for Bcl2.

Conclusions: These data suggest that VSMC chronically exposed to a hyperglycemic media as a DNA damage inductor can modify the expression of classic apoptosis pathway proteins, entering into a stationary repair phase. By maintaining the detrimental stimulus the equilibrium between pro and antiapoptosis persist, and at the end of the damage repair phase the cell would continue a potentiated growth induced by the antiapoptosis proteins of the Bcl2 family, which would promote less cell death and a greater cellular proliferation. This alteration could explain the vascular remodeling anomalies described earlier.

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