Potential Role of the Early Response Gene c-myc in β-Cell Adaptation to Changes in Glucose Concentration

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Type 2 diabetes is characterized by a reduction in both insulin sensitivity and glucose-stimulated insulin secretion (GSIS). Although insulin resistance usually precedes β-cell dysfunction, the role of the latter in the development of the disease is unclear. The detrimental effect that chronic hyperglycemia exerts on β-cell function is well established and may contribute to further deterioration of GSIS during development of type 2 diabetes. Islets from hyperglycemic 90%-pancreatectomized rats display profound alterations in GSIS and β-cell gene expression. The association of these changes with β-cell hypertrophy and increased mRNA levels of the early response gene c-myc could reflect a loss of β-cell differentiation (1). The complete reversal of all these abnormalities upon correction of hyperglycemia suggested hyperglycemia as their triggering factor. The aim of this study was to determine whether glucose directly regulates islet c-myc expression. Rat islets were cultured for 1–7 days in RPMI medium containing 5, 10, 20, or 30 mmol/l glucose (G5–G30) and 0.5% bovine serum albumin. Islet c-myc and TATA box binding protein (TBP) mRNA levels were measured by semiquantitative reverse transcriptase–polymerase chain reaction. As compared with freshly isolated islets from the same preparation, the ratio of c-myc to TBP was increased approximately fivefold after overnight culture. This increase persisted after 3–7 days in G5. In contrast, the c-myc–to–TBP ratio returned to control values after 7 days in G10–G30. To avoid the confounding effect of the early increase in c-myc mRNA, probably due to stress of isolation, islets were first cultured for 7 days in G10 and then overnight in G5–G30. When the glucose concentration was kept at 10 mmol/l, the c-myc–to–TBP ratio remained low and stable, whereas an approximate fivefold increase was observed after 1 day at either lower or higher glucose. In contrast, c-myc heterodimerization partner Max and its partner Mad1 were not affected by culture or glucose. The increase in islet c-myc–to–TBP ratio produced by high glucose was confirmed in rats maintained hyperglycemic (blood glucose >11 mmol/l) for 1–4 days by glucose clamp (~200% of saline-infused rats). In contrast, fasting for 3 days reduced blood glucose to 3 mmol/l and modestly increased islet c-myc–to–TBP ratio to 132% of the ratio in fed rats. These results strongly suggest that both low and high glucose increase islet c-myc expression. Whereas the increase in low glucose could be related to the higher rate of apoptosis reported under this condition, the increase produced by high glucose could play a role in β-cell mass adaptation to hyperglycemia (replication/hypertrophy).

REFERENCES


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GSIS, glucose-stimulated insulin secretion; TBP, TATA box binding protein.