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When sugar is not so sweet: glucose toxicity.

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Editorial

Increased glucose levels activate insulin secretion and increase insulin gene transcription and synthesis. The release of insulin rapidly corrects the hyperglycemia. A fact which has become increasingly clear over the last decade is that even brief periods of chronic hyperglycemia can impair the compensatory adaptions in secretion, synthesis, and action of insulin. These observations form the basis of the important concept of glucose toxicity (1). The clinical counterpart to this concept is the observation that normalization of blood glucose levels by diet, sulfonylureas, or intensive insulin treatment in non-insulin-dependent diabetes augments insulin secretion, improves glucose disposal, and facilitates subsequent diabetic management. Improved insulin secretion during the honeymoon period of insulin-dependent diabetes may also represent reversal of glucose toxicity.

Studies by Olson et al. using HIT cells, an SV 40 transformed insulin-secreting cell line, provide insight into the potential mechanisms by which chronic hyperglycemia impairs β-cell function (2). HIT cells release insulin in response to all secretagogues including glucose. However, with time in culture, these cells lose the ability to secrete insulin in response to a glucose stimulus. Insulin content and insulin mRNA levels fall in parallel with this acquired secretory defect. These effects of glucose on insulin secretion and synthesis are partially aborted by growing the cells at low glucose concentrations (3), suggesting this cell line might be a model for glucose toxicity.

Gene transcription is controlled by factors which bind to specific regulatory regions of DNA. The results of Olson et al. suggest that chronic hyperglycemia lowers the amount of a specific transcription factor that may regulate the insulin gene. In nuclear extracts of HIT cells, the authors identified a factor (named glucose-dependent transcription factor) which binds specifically to two sites on the DNA of the human insulin promoter, known as CT1 and CT2. These same DNA binding sites interact with another transcription factor, IUF-1, that is enriched in insulinoma cells (4). Mutational analysis has established that these sites are important for the full activity of the human insulin gene promoter. Glucose-dependent transcription factor was not present in nuclear extracts of HIT cells grown at high glucose concentrations. Furthermore, mutations of these sites confirmed their importance for human insulin promoter transcriptional activity. The results in this paper, however, must be interpreted with caution. The assay used in this study only measures binding to this region. Direct proof that this factor regulates insulin gene transcription, and is responsible for a decline in transcription rate, cannot be definitively assigned to these sequence elements. If the loss of a specific binding species is causal in reducing insulin gene transcription at high glucose concentrations, the mechanisms still might not be directly related to glucose. For example, the metabolic rate or rapidity of cell growth may be reduced in the cells grown at low glucose levels. If this were the case, the passage number may not be an adequate way to compare the overall growth or the specific cell-cycle environment between cells grown under such radically different metabolic conditions.

German et al. have identified a 50 base sequence of the rat insulin I gene that acts like a glucose-sensitive element and contains the cognate element described by Olson et al. (5). Transfection experiments with fetal rat islet cultures revealed that this element enhances the activity of heterologous promoters as a function of the glucose level. However, in the HIT cell, this glucose sensitive region could not be mapped by systematic mutational analysis of the rat insulin promoter. Thus, a direct connection between the acute activation of the insulin gene by systematic glucose and loss of insulin gene transcriptional activity during chronic hyperglycemia remains an open issue. The major question generated by these important observations is: can the data in HIT cells be extrapolated to the toxic effects of glucose observed in diabetic humans? These are transformed cells and the results should be extended to normal tissue like pancreatic islets to strengthen the hypothesis. Culturing isolated human islets at high glucose levels decreases insulin secretion, proinsulin biosynthesis, and insulin content (6). Although islets contain a mixture of cell types, if the glucose-dependent transcription factor is found only in β-cells, it might be possible to confirm these results in human islets and more clearly establish a link to the important phenomenon of glucose toxicity.

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