Glucose Regulates Acetyl-CoA Carboxylase Gene Expression in a Pancreatic $\beta$-Cell Line (INS-1)*

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Glucose has pleiotropic actions on the pancreatic $\beta$-cell. An elevation in plasma glucose promotes the release of insulin (1, 2) and activates insulin gene transcription (3) and proinsulin mRNA translation (3). Glucose has also trophic effects on the endocrine pancreas as it stimulates both in vivo and in vitro $\beta$-cell DNA synthesis and multiplication (4–6). In addition, prolonged hyperglycemia causes $\beta$-cell hyperplasia and hypertrophy (6–8) with a resulting hyperinsulinemia (6–8). Little is known about the molecular nature and the genes implicated in the late phenotypic changes induced by glucose. Since glucose must be metabolized to induce the release of insulin, it is reasonable to hypothesize that the expressions of some key regulatory enzymes of intermediate metabolism are modulated by this carbohydrate in the $\beta$-cell. Using pancreatic islets, glucose has been documented to increase pyruvate dehydrogenase (E1$\alpha$ subunit) and pyruvate carboxylase mRNAs (9), to decrease the branched chain keto acid dehydrogenase E1$\alpha$ subunit mRNA (10), and to cause the accumulation of a number of islet proteins of unknown functions (11, 12).

Since the trophic actions of glucose must be accompanied by accelerated protein and de novo lipid biosynthesis, it would be of interest to assess whether some genes encoding enzymes in the lipid biosynthetic pathway are glucose-inducible in the $\beta$-cell. This question is also of interest in relation to the long term effects of glucose on insulin release, since we have provided much experimental evidence supporting the concept that malonyl-CoA and long chain acyl-CoA esters act as metabolic coupling factors when $\beta$-cells are stimulated by nutrient secretagogues (13–15). Among the enzymes of lipid metabolism, acetyl-CoA carboxylase (ACC) plays a pivotal role since it catalyzes the rate limiting step of lipid biosynthesis and its product, malonyl-CoA, controls the rate of fatty acid oxidation (16). ACC displays both short and long term regulation. It is acutely controlled by phosphorylations on Ser/Thr residues and by allosteric interactions with a number of metabolites including citrate, malonyl-CoA, and long chain acyl-CoA esters (17). Long term control in vivo by dietary manipulations (18) and in vitro by nutrients (19, 20) and hormones (19, 21) is mainly exerted by changes in ACC gene expression. Molecular studies of the ACC gene revealed that ACC is expressed from two promoters from a single copy gene (22). The ACC primary transcripts are differentially spliced to produce at least five mRNAs that differ only in their 5'-untranslated region (22).

The field of pancreatic $\beta$-cell gene expression has been markedly hampered by the limited amount of biological material which can be obtained from pancreatic islets and the cellular heterogeneity of the tissue. Various insulin secreting cell lines that have been used to date do not show biological actions of glucose in the physiological range and may therefore not be appropriate models for studies of the long term effects of glucose on the pancreatic $\beta$-cell. A new cell line (INS-1) has recently been obtained by Asfari et al. (23) in our division. INS-1 cells are well differentiated and they contain 20% of the amount of insulin of normal rat $\beta$-cells (23). Glucose in the physiological range promotes insulin secretion (23) and increases the cellular redox state (24) at least in part through $Ca^{2+}$ activation of mitochondrial glycerol-phosphate dehydrogenase (25). This cell line may thus provide an interesting tool for a variety of aspects of islet research.

*The abbreviations used are: ACC, acetyl-CoA carboxylase; PAGE, polyacrylamide gel electrophoresis; PMA, phorbol 12-myristate 13-acetate; bp, base pair.
As a first step toward a better understanding of the action of various nutrients on the expression of metabolic enzymes involved in the pathway of malonyl-CoA formation from glucose, we believe plays important role in β-cell fuel sensing (13–15, 26) we chose to study the effect of glucose on ACC gene expression. Using INS-1 cells as a model, we show that glucose in the physiological range is a major regulator of the ACC gene in β-cells and that the signal transduction systems implicated in ACC induction are entirely different from those involved in insulin secretion.

EXPERIMENTAL PROCEDURES

Cell Culture and Incubations—INS-1 cells were grown in monolayer cultures as described previously (23) in RPMI 1640 medium containing 11.2 mM glucose supplemented with 10 mM HEPES, 10% heat-inactivated fetal calf serum, 2 mM L-glutamine, 100 IU/ml penicillin, 100 μg/ml streptomycin, 1 mM sodium pyruvate, and 50 μM β-mercaptoethanol at 37 °C in a humidified (5% CO2, 95% air) atmosphere. Cells were seeded 7 days before use in 95-cm2 Petri dishes at a density of 1.4 X 106 cells per culture dish. When INS-1 cells reached approximately 80% confluency, they were washed twice with 11 mM phosphate-buffered saline (pH 7.0, 37 °C) and preincubated for 20 h at 37 °C in culture medium containing 5 mM glucose. Following preincubation, cells were incubated in the presence of various nutrients and test substances.

Insulin Secretion and Biochemical Measurements—INS-1 cells were plated (1.4 X 105 cells/well) into 24-well plates (Falcon) and cultured for 7 days. Two days prior to insulin secretion measurements, cells were cultured at 5, 11, and 20 mM glucose. Following preincubations at various glucose concentrations, cells were washed twice with a Krebs-Ringer bicarbonate medium containing 1 mM CaCl2, 5 mM NaHCO3, 25 mM HEPES (pH 7.4), and 0.07% bovine serum albumin and preincubated for 30 min at 37 °C in 1 ml of Krebs-Ringer bicarbonate medium in the presence of 5 mM glucose. Cells were then incubated for an additional 30 min in the presence of various secretagogues. After incubation, incubation media were collected and insulin secretion was determined by radioimmunoassay, using a guinea pig anti-porcine insulin antibody and rat insulin as a standard (15). The total cellular insulin contents were measured after acid-ethanol (concentrated HCl (1.5%), ethanol (75%)) extraction of cells. For the measurement of cellular glucose 6-phosphate content, INS-1 cells were plated in 95-cm2 Petri dishes and incubated as described in the legend to Fig. 8. Glucose 6-phosphate was measured using a fluorometric assay following protein extraction with 0.6 M HClO4 (27).

ACC mRNA and Protein Analysis—Total RNA was extracted from cells by the guanidium isothiocyanate method (28). RNA samples (12 μg) were denatured by incubation in glyoxal, subjected to electrophoresis in 0.7% agarose gels, and electrotransferred to a nylon membrane. ACC mRNA sequences were detected by Northern blot hybridization with 32P-labeled cRNA probes (29). The linearized plasmids used were: pGEM3-ACC (containing the 509-bp EcoRI–EcoRI fragment of ACC clone P181-6 (30)) and pSP65-actin (containing the 720-bp PstI–PvuII fragment of the coding region of a human actin cDNA (31)). Membranes were exposed for autoradiography at −70 °C using pre-flashed x-ray film (Fuji). Total proteins were determined using the Coomassie Blue method (Bio-Rad). Materials—Hybond-N nylon membranes, [32P]UTP, 125I-labeled donkey anti-rabbit IgG antibody, and 125I-streptavidin were purchased from Amersham Corp. Nitrocellulose membranes were obtained from Schleicher & Schuell. All other biochemicals were of analytical grade.

RESULTS

Elevation of medium glucose from 5 to 20 mM caused a marked accumulation of ACC mRNA (Fig. 1). The lag time of the induction was comprised between 3 and 4 h. High glucose caused a 4-fold induction of ACC transcript after 4–6 h of incubation. A maximal 15–20-fold accumulation of ACC mRNA occurred at 24 h of incubation.

Examination of the dose dependence of the effect of glucose (Fig. 2) indicated that the threshold concentration of the sugar was 5–8 mM. Half-maximal and maximal inductions occurred at 15 and 20 mM glucose, respectively.

To determine whether glucose-induced ACC mRNA accumulation bears physiological relevance for the β-cell, we determined ACC protein levels following a 72-h incubation of INS-1 cells at different glucose concentrations. The results indicated that ACC mRNA induction was associated with ACC protein accumulation (Fig. 3). The dose responses of glucose-induced ACC mRNA and protein accumulation were qualitatively and quantitatively similar. It can be concluded that induction of the transcript can fully account for the accumulation of the ACC protein.

To assess whether high glucose causes a generalized or selective metabolic enzyme induction, we determined in the same experiment its action on two carboxylating enzymes, i.e. ACC and pyruvate carboxylase. For this purpose, we separated INS-1 cell protein on a 5% SDS polyacrylamide gel, blotted the proteins on a cellulose membrane, and incubated the membranes with 125I-streptavidin which recognizes biotin-flashed x-ray film (Fuji). Total proteins were determined using the Coomassie Blue method (Bio-Rad). Materials—Hybond-N nylon membranes, [32P]UTP, 125I-labeled donkey anti-rabbit IgG antibody, and 125I-streptavidin were purchased from Amersham Corp.Nitrocellulose membranes were obtained from Schleicher & Schuell. All other biochemicals were of analytical grade.

FIG. 1. Time course of glucose-induced ACC mRNA induction. INS-1 cells were incubated at 5 mM or 20 mM glucose as described under "Experimental Procedures." Following the indicated incubation times, total RNA was isolated and ACC mRNA transcript was measured by Northern blot hybridization with 32P-labeled cRNA probe. Membranes were rehybridized with an actin cRNA probe to control the amount of RNA present in each lane (12 μg of RNA). The upper panel shows a Northern hybridization signal of ACC clone P181-6 (30) and pSP65-actin (containing the 720-bp PstI–PvuII fragment of the coding region of a human actin cDNA (31)). Membranes were exposed for autoradiography at −70 °C using pre-flashed x-ray film (Fuji). Total proteins were determined using the Coomassie Blue method (Bio-Rad). Materials—Hybond-N nylon membranes, [32P]UTP, 125I-labeled donkey anti-rabbit IgG antibody, and 125I-streptavidin were purchased from Amersham Corp. Nitrocellulose membranes were obtained from Schleicher & Schuell. All other biochemicals were of analytical grade.

FIG. 2. Elevation of medium glucose from 5 to 20 mM caused a marked accumulation of ACC mRNA (Fig. 1). The lag time of the induction was comprised between 3 and 4 h. High glucose caused a 4-fold induction of ACC transcript after 4–6 h of incubation. A maximal 15–20-fold accumulation of ACC mRNA occurred at 24 h of incubation.

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values there are no other known biotin-containing proteins in this range (32). In contrast to ACC protein, glucose did not alter INS-1 cell pyruvate carboxylase level. This indicates that the action of glucose is selective and does not reflect a general induction of metabolic enzymes. It is noteworthy that MacDonald et al. (9) showed that glucose caused pyruvate carboxylase mRNA accumulation in pancreatic islets. However, pyruvate carboxylase protein was not measured, and the effect was small above 5 mM glucose (30% increase in ACC enzyme activity) (9). It may be that pyruvate carboxylase mRNA induction by glucose is not associated with accumulation of pyruvate carboxylase protein. Alternatively rat islets and clonal β-cells (INS-1) may be different in this respect.

The labeled streptavidin revealed two bands (Fig. 4). The band of 260,000 is ACC. The protein of 120,000 is most likely pyruvate carboxylase (PC). In contrast to ACC protein, glucose did not alter INS-1 cell pyruvate carboxylase level. This indicates that the effect of glucose on the steady state levels of ACC mRNA cannot be accounted for by changes in RNA turnover. To assess the latter possibility, we determined the half-life of ACC mRNA in islets incubated at 20 mM glucose (9). It may be that pyruvate carboxylase mRNA induction by glucose is not associated with accumulation of pyruvate carboxylase protein. Alternatively rat islets and clonal β-cells (INS-1) may be different in this respect.

The glucose-induced accumulation of ACC mRNA might result from alterations in transcription rate and/or in mRNA turnover. To assess the latter possibility, we determined the half-life of ACC mRNA in islets incubated at 20 mM glucose (9). It may be that pyruvate carboxylase mRNA induction by glucose is not associated with accumulation of pyruvate carboxylase protein. Alternatively rat islets and clonal β-cells (INS-1) may be different in this respect.

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Phosphorylated by glucokinase (34). 2-Deoxyglucose induced ACC mRNA, although to a lesser extent than glucose, whereas and \(-\)cell type transporter GLUT 2 (35) but cannot be phosphorylated by glucokinase (34). 2-Deoxyglucose induced ACC mRNA, although to a lesser extent than glucose, whereas 3-O-methylglucose and 6-deoxyglucose were ineffective (Fig. 6). These observations are similar to the one reported previously by Foufelle et al. (37) in the adipocytes.

Among all the metabolizable nutrients that we tested, only the glucose epimer mannose (Fig. 6) induced ACC mRNA. The following classes of compounds were tested which did not alter ACC mRNA levels (see also Fig. 6): 1) amino acids: L-glutamine (10 mM), L-leucine (10 mM), L-glutamine (10 mM) plus L-leucine (10 mM), L-arginine (10 mM), pyruvate (15 mM); 2) carboxylic acids, alcohols, ketones, aldehydes: dihydroxyacetone (10 mM), glyceraldehyde (10 mM), 2-ketoisocaproate (10 mM), L-lactate (10 mM), glycerol (10 mM); 3) hexoses and related substances: N-acetyl-D-glucosamine (30 mM), glucosamine (30 mM), fructose (20 mM), galactose (20 mM), mannitol (20–40 mM); 4) pentoses: D-arabinose (20 mM), D-ribose (20 mM); 5) disaccharides: lactose (20 mM), sucrose (20–40 mM), maltose (20 mM); 6) fatty acids: myristate, palmitate, linoleate, arachidonate (0.36 mM), oleate (1 mM), in the presence of bovine serum albumin (0.5 g/100 ml). Among the compounds tested, leucine, glutamine plus leucine, arginine, 2-ketoisocaproate, N-acetylglycosamine, glucosamine, and fructose are insulin secretagogues (1) but had no effect on ACC mRNA. The results indicate a relatively high degree of specificity of glucose, its nonmetabolizable analogue 2-deoxyglucose, and its epimer mannose in the ACC mRNA induction process.

The Ca\(^{2+}\)-calmodulin, CAMP, and protein kinase C transduction systems are thought to mediate the action of nutrients on insulin release (13, 36). To test whether these pathways are implicated in ACC mRNA induction, we examined the action of a high concentration of K\(^+\) which markedly elevates intracellular Ca\(^{2+}\) (13, 36), the adenylated cyclase activator forskolin, and the phorbol ester phorbol 12-myristate 13-acetate (PMA) which activates C-kinase enzymes (13). These compounds promoted insulin release under our experimental conditions (not shown) yet did not modify ACC mRNA level of INS-1 cells. This demonstrates that the Ca\(^{2+}\), CAMP, and C-kinase signaling pathways do not mediate the action of glucose on the ACC gene.

To gain insight into the mechanism of the glucose-induced ACC mRNA accumulation, we tested mannoheptulose, a specific inhibitor of glucokinase (34). Mannohexulose suppressed the stimulatory effect of glucose on insulin release (not shown) and ACC mRNA accumulation (Fig. 7), suggesting that the sugar needs to be phosphorylated by glucokinase to exert its effect. Similar observations were made (not shown) with glucosamine which inhibits glucokinase (34). Forskolin (Fig. 7) and 8-bromo-CAMP (not shown) markedly inhibited ACC mRNA induction by glucose, whereas high K\(^+\) or PMA did not (not shown). These observations indicate that the ACC gene, which contain a cAMP-responsive element in promoter 2 (21, 22), is negatively modulated by the CAMP-signaling pathway, whereas the Ca\(^{2+}\) and C-kinase transduction system do not participate in ACC gene regulation in INS-1 cells.

Consistent with the concept that the phosphorylation of glucose is required for ACC gene induction and that glucose 6-phosphate may mediate the action of the sugar, glucose caused a dose-dependent rise in the glucose 6-phosphate content of INS-1 cells (Fig. 8). Furthermore, mannohexulose and glucosamine suppressed the effects of glucose on both the glucose 6-phosphate content (Fig. 8) and ACC mRNA (Fig. 7).

Are changes in ACC protein content associated with modification in glucose-induced insulin release? Fig. 9 indicates that preincubating cells at various glucose concentrations ranging from 5 to 20 mM during 48 h did not modify maximal insulin release promoted by glucose (20 mM). However, preincubating cells at 5, 11, and 20 mM glucose resulted in low, intermediate, and high basal insulin release, respectively. The optimal glucose concentration during preincubation in term of glucose-induced insulin release was 5 mM. This finding is of great interest since it shows that a pancreatic \(-\)cell line (INS-1) can release insulin in response to variations in glucose within the physiological range. The extent of glucose stimulation is similar to that of isolated pancreatic islets, provided that cells are preincubated at a physiological basal concentration of glucose (5 mM).

A close relationship was observed between basal insulin release and ACC protein content of INS-1 cells (Fig. 10). This observation strengthens the view that ACC is one of the pace-
setting enzymes of metabolic signal transduction in the pancreatic β-cell.

DISCUSSION

Previous work from our laboratory has provided support for the concept that malonyl-CoA acts as a metabolic coupling factor in nutrient-induced insulin release (13-15). This concept is teleologically attractive because it implies that the same metabolite, i.e. malonyl-CoA, which rises in the target tissues of insulin to decrease the oxidation of fatty acids and favor nutrient storage (16), also rises in the pancreatic β-cell to cause the release of the fuel storage hormone insulin. Since the flux through ACC controls malonyl-CoA levels (16, 17), ACC might be like glucokinase for glucose (2), a key nutrient sensor in the β-cell. Therefore, studying both the short and long term regulation of ACC in the β-cell should contribute to our understanding of the true function of this key regulatory enzyme in β-cell physiology.

In the present report we have shown that glucose is a major regulator of ACC gene expression in clonal pancreatic β-cells (INS-1). The effect is relatively rapid since the lag time of ACC mRNA induction by glucose lies between 3 to 4 h. The action of the sugar is quantitatively important as it caused a 15-20-fold induction in both ACC protein and mRNA. It is noteworthy that glucose caused the accumulation of ACC protein and mRNA only above 5 mM. This demonstrates that the action of glucose occurs only at physiological concentrations of the sugar and that it does not reflect an unspecific fuel repletion induction. Indeed at 11 mM glucose, the ACC protein content of INS-1 cells was approximately 5-fold of that observed at 5 mM (Fig. 10). In addition, our unpublished work indicates that pancreatic islets obtained from 48-h fasted animals refed a high carbohydrate diet for 72 h show marked induction of ACC mRNA. The action of glucose on ACC protein and mRNA showed identical dose dependencies and were quantitatively similar. Moreover, glucose did not modify the stability of the ACC transcript. Thus, glucose induction of ACC most likely occurs at the transcriptional level. This remains to be directly demonstrated.

By simple analogy with nutrient regulation of insulin secretion, we initially thought that post glycolytic metabolites might mediate the action of glucose on ACC induction and that the Ca2+, cAMP, and diacylglycerol/C-kinase pathways might be implicated in the induction process (13). Using similar thinking Collins et al. (11, 12) have proposed several criteria to be met for a protein to qualify as a pancreatic β-cell glucose-response protein, including one stating that the effect of glucose should be mimicked by the secretagogue 2-ketoisocaproate. Surprisingly, we found a remarkable specificity of the action of glucose on ACC mRNA/protein induction. Among the many tested carbohydrates, keto acids, amino acids, and fatty acids, only mannose mimicked the action of glucose. In addition, activation of the Ca2+, cAMP, and C-kinase pathways with high K+, forskolin, and PMA, respectively, did not induce ACC mRNA. These observations imply three important conclusions: 1) glucose does not need to be metabolized beyond glucose 6-phosphate in the glycolytic pathway to induce ACC mRNA; 2) the metabolic coupling factors and signal transduction systems that mediate the action of glucose to cause insulin release are entirely different from those implicated in the induction of the ACC gene; and 3) different nutrient secretagogues should not necessarily induce the same proteins.

We are now left with interesting questions about the mode

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Footnotes:

1. T. Brun, E. Roche, K.-H. Kim, and M. Prentki, unpublished data.
of action of glucose on ACC gene induction. Namely, does glucose itself or one of its metabolites cause ACC mRNA accumulation, and what are the ACC gene regulatory sequences and associated proteins implicated in the process? Since 2-deoxyglucose is effective and the actions of glucose on both ACC mRNA and the glucose 6-phosphate content of INS-1 cells are suppressed by the glucokinase inhibitors mannoheptulose and glucosamine, it is likely as suggested before in the adipocytes (37) that glucose 6-phosphate mediates the effect. Consistent with the view that glucose 6-phosphate mediates ACC gene induction by glucose, glucose caused a dose-dependent rise in the glucose 6-phosphate content of INS-1 cells. Carbohydrate response elements have recently been identified in the L-type pyruvate kinase and S14 gene promoters (38-42). Comparison of the sequences conferring carbohydrate regulation revealed a segment with 9 out of 10 nucleotides identity (42). The conserved motif contained the sequence 5'-CACGTG-3' which has similarity to the core sequence CTC(A/C)CGT confers glucose induction to the three pancreatic islet physiology. First, increased ACC expression may be a model gene for studies aiming at a better understanding of the action of glucose on pancreatic β-cell gene expression and the long term adaptive responses of β-cells to chronic elevations in glucose and other nutrients.

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