Phosphoenolpyruvate carboxykinase (PEPCK) is a rate-controlling enzyme in hepatic gluconeogenesis, and it therefore plays a central role in glucose homeostasis. The rate of transcription of the PEPCK gene is increased by glucagon (via cAMP and glucocorticoids) and is inhibited by insulin. Under certain circumstances glucose also decreases PEPCK gene expression, but the mechanism of this effect is poorly understood. The glucose-mediated stimulation of a number of glycolytic and lipogenic genes requires the expression of glucokinase (GK) and increased glucose metabolism. HL1C rat hepatoma cells are a stably transfected line of H4IE rat hepatoma cells that express a PEPCK promoter-chloramphenicol acetyltransferase fusion gene that is regulated in the same manner as the endogenous PEPCK gene. These cells do not express GK and do not normally exhibit a response of either the endogenous PEPCK gene, or of the trans-gene, to glucose. A recombinant adenovirus that directs the expression of glucokinase (AdCMV-GK) was used to increase glucose metabolism in HL1C cells to test whether increased glucose flux is also required for the repression of PEPCK gene expression. In AdCMV-GK-treated cells glucose strongly inhibits its hormone-activated transcription of the endogenous PEPCK gene and of the expressed fusion gene. The glucose effect on PEPCK gene promoter activity is blocked by 5 mM mannoheptulose, a specific inhibitor of GK activity. The glucose analog, 2-deoxyglucose mimics the glucose response, but this effect does not require GK expression. 3-O-methylglucose is ineffective. Glucose exerts its effect on the PEPCK gene within 4 h, at physiologic concentrations, and with an EC_{50} of 6.5 mM, which approximates the \( K_m \) of glucokinase. The effects of glucose and insulin on PEPCK gene expression are additive, but only at suboptimal concentrations of both agents. The results of these studies demonstrate that, by inhibiting PEPCK gene transcription, glucose participates in a feedback control loop that governs its production from gluconeogenesis.

Phosphoenolpyruvate carboxykinase (PEPCK); EC 4.1.1.32

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\(^\dagger\) The abbreviations used are: PEPCK, phosphoenolpyruvate carboxykinase; S14, spot 14; GK, glucokinase; Glu-6-P, glucose 6-phosphate; dexamethasone/cAMP, dexamethasone and 8-(-chlorophenylthio)cAMP; ChoRE, carbohydrate response element; CAT, chloramphenicol acetyltransferase; \( \beta \)-Gal, \( \beta \)-galactosidase.
Glucose Inhibition of PEPCK Gene Expression

a reporter gene driven by the pyruvate kinase gene promoter in the absence of insulin when isolated hepatocytes are cotransfected with a vector that expresses GK (21). Likewise, the fatty acid synthase gene can be induced by glucose in hepatocytes that have been pre-treated with hormones (including insulin) that stimulate GK gene expression (22). The mechanism of glucose action on these genes is not fully understood. However, the metabolism of glucose is required since metabolizable analogs of glucose mimic the effect, whereas nonmetabolizable analogs do not (15). Thus, it is thought that a metabolite of glucose confers a signal that results in the altered expression of a number of genes involved in the regulation of glucose and lipid metabolism (13–16).

Glucose decreases hormone-activated PEPCK gene expression in primary hepatocytes and Fao hepatoma cells, but fails to regulate PEPCK in H4IIE cells (9, 12). This difference in the ability of glucose to regulate PEPCK gene expression may reflect the intrinsic glucose phosphorylating capacity in the different cells. In the present study, we test the hypothesis that an increase in glucose metabolism allows glucose to repress hormone-activated PEPCK gene transcription in cells that do not normally respond to glucose. HL1C rat hepatoma cells were used, a cell line that is a derivative of H4IIE cells that affords the direct measurement of PEPCK promoter activity and that does not express GK. We find that the inhibition of glucocorticoid- and cAMP-stimulated PEPCK gene transcription by glucose in these cells is dependent on GK expression, controlled in this study by exposure of the cells to a recombinant adenovirus that contains the GK cDNA (23). This inhibition by glucose correlates closely with GK activity and glucose metabolism. In addition, physiologic concentrations of glucose inhibit PEPCK gene promoter activity within 4 h. This effect is independent of insulin and is additive with this hormone at suboptimal concentrations of both agents.

EXPERIMENTAL PROCEDURES

Cell Culture, Treatment with Recombinant Adenovirus, and CAT Assays—The isolation of the H4IIE rat hepatoma-derived stable transfectant, IC, was described previously (24). This cell line contains the PEPCK promoter segment from −2100 to +69, relative to the transcription start site, ligated to the CAT reporter gene. The maintenance of H4IIE and HL1C cells and the measurement of CAT activity have been described previously (25–27). Cells were treated with an appropriate volume (see below) of recombinant adenovirus in fresh Dulbecco’s modified essential medium supplemented with 2.5% newborn calf serum and 2.5% fetal bovine serum for 30–36 h prior to treatment with hormones and/or glucose or mannitol. Hormone and sugar or sugar alcohol treatments were carried out in serum and glucose free Dulbecco’s modified essential medium supplemented with 1 mM sodium pyruvate. In addition, the medium was adjusted, as needed, with various concentrations of mannitol so that it always contained at least 5.0 mM glucose or mannitol to avoid hypo-osmotic conditions.

Preparation of Recombinant Adenovirus—Recombinant adenoviruses containing the cDNAs encoding the rat liver glucokinase (AdCMV-GK) (23) and the Escherichia coli β-galactosidase (AdCMV-β-Gal) (28) genes were prepared from 293 human embryonal kidney cell lines, as described previously (23). A titer of AdCMV-GK virus was established so that a given volume of clarified lysate inhibited dexamethasone/cAMP-stimulated PEPCK gene promoter activity from semiconfluent HL1C cells in a 100-cm² dish by 70–80%, as measured by CAT activity. Likewise, a titer of AdCMV-β-Gal virus was established such that a given volume of lysate stained 80% of a monolayer of HL1C cells after fixation and treatment with 5-bromo-4-chloro-3-indoly-β-D-galactopyranoside (29).

RNA Isolation and Primer Extension Analysis—The synthesis of the PC28 and ACT25 oligonucleotides was accomplished as described previously (30). These oligonucleotides are complimentary to the mRNAs of the rat PEPCK and rat β-actin genes at positions 102–129 and 42–67, respectively (31, 32). Total RNA was isolated with Tri-Reagent (Molecular Research Center, Inc., Cincinnati, OH) using the instructions provided by the manufacturer. A primer extension assay was used to measure PEPCK and β-actin mRNA amounts, as described previously (24). The products of the primer extension assay were quantified using a Bio-Rad GS-20 Molecular Imager in conjunction with the Bio-Rad Molecular Analyst software.

Enzyme and Metabolic Assays—Glucose phosphorylating activities were measured by a radioisotopic assay using ([U-14C]glucose in whole cell extracts in the presence of 10 mM glucose 6-phosphate (Glu-6-P) to distinguish between low Km, Glu-6-P-sensitive hexokinase activities and GK activity (33). Glucose usage was measured in intact cells using [2-3H]glucose and the subsequent production of 3H2O as described previously (34, 35). Lactate accumulation was determined using a colorometric assay kit (Sigma).

RESULTS

AdCMV-GK Increases Glucose Metabolism in HL1C Cells—HL1C cells are a stable transfectant of H4IIE rat hepatoma cells that express the CAT reporter gene driven by the PEPCK promoter from −2100 to +69 relative to the transcription start site. CAT gene expression in this system reflects the hormonal regulation of the endogenous PEPCK gene in that transcription of the fusion gene is strongly induced (20–50-fold) by the combination of dexamethasone/cAMP, and this response is inhibited by insulin (24, 30). The ability of glucose to alter the expression of a number of glucose-responsive genes requires GK activity in order to increase glucose metabolism (13–16). Intermediary metabolites of either glycolysis or the pentose phosphate shunt, as well as Glu-6-P, have been implicated as potential mediators of the signal generated by glucose in the liver (22, 36). Although derived from hepatocytes, HL1C cells have no intrinsic GK activity and do not respond to glucose (data not shown and see Fig. 1). Therefore, HL1C cells were treated with a recombinant adenovirus that expresses rat liver GK (AdCMV-GK) to test whether this treatment increases glucose metabolism and, if so, whether increased glucose metabolism has an affect on hormone-activated PEPCK gene promoter activity. HL1C cells treated with AdCMV-GK and incubated in 3 mM glucose displayed a 2.5-fold increase in glucose utilization over control cells, as measured by 3H2O production.
generated from $[2^{-3}H]$glucose. This effect increased to 6-fold when the cells were incubated in 20 mM glucose. Similarly, lactate accumulation was increased about 2-fold when the cells treated with AdCMV-GK were incubated in 3 mM glucose and was markedly increased when 20 mM glucose was used in the medium (Table I). In contrast, cells treated with a recombinant adenovirus that expresses the E. coli β-galactosidase gene (AdCMV-β-Gal) exhibited levels of glucose utilization and lactate accumulation about equal to untreated control cells in the presence of either 3 or 20 mM glucose (Table I). These data demonstrate that infection of HL1C cells with AdCMV-GK leads to the expression of GK and a subsequent increase in glucose metabolism. Furthermore, the increase in glucose metabolism is not due to adenoviral infection alone, since infection with AdCMV-β-Gal had no affect on glucose metabolism.

Glucose Represses PEPCK Gene Transcription in a GK-dependent Manner—We tested whether elevated concentrations of glucose could inhibit hormone-activated, PEPPK promoter-driven, CAT expression in AdCMV-GK-treated HL1C cells and, if so, whether this effect was dependent on the expression of GK. Untreated cells, or cells treated with either AdCMV-β-Gal or AdCMV-GK, were treated with dexamethasone/cAMP and challenged with high concentrations of glucose or mannitol. A 12-h treatment with 20 mM glucose decreased the dexamethasone/cAMP activation of the PEPPK-CAT fusion gene by 80% in cells that express GK (Fig. 1). In contrast, CAT activity was not affected by the elevated glucose concentration in control cells or in cells treated with AdCMV-β-Gal. Together, these observations indicate that the glucose effect on PEPPK gene promoter activity is dependent on the expression of GK. Additionally, treatment with adenovirus per se had no effect on PEPPK gene promoter activity, since cells treated with AdCMV-β-Gal did not respond to elevated concentrations of glucose. Furthermore, 20 mM mannitol had no effect on the dexamethasone/cAMP response slightly (about 20%) and the same concentration of mannheptulose blocked the inhibition by glucose. One mM insulin decreased the dexamethasone/cAMP response by 75%, and did so in the absence of glucose. This confirms previous observations which demonstrated that the insulin effect on PEPPK gene promoter activity is independent of glucose (8, 9) (see also Fig. 7 below). Mannoheptulose did not relieve the insulin-mediated inhibition of hormone-stimulated CAT expression in these cells, which demonstrates the specificity of its effect. Together, these data demonstrate that glucose inhibits hormone-activated PEPPK promoter activity in HL1C cells in a GK-dependent manner.

Glucose Represses the Expression of the Hormone-activated Endogenous PEPPK Gene in H4IIE Cells Treated with AdCMV-GK—H4IIE rat hepatoma cells, the parental cell line of HL1C cells, were treated with AdCMV-GK or AdCMV-β-Gal to test whether the hormone-activated endogenous PEPPK gene could also be repressed by glucose. Primer extension experiments were performed to measure mRNAPEPPK (Fig. 4). An overnight treatment with dexamethasone/cAMP increased mRNAPEPPK by about 9-fold, in agreement with previous results (30). Mannitol had no affect on the induction of mRNAPEPPK by dexamethasone/cAMP. However, the presence of 20 mM glucose in the culture media blunted the dexamethasone/cAMP effect in untreated cells, and in cells treated with AdCMV-β-Gal, by 40 and 35%, respectively. This is in contrast with the observation that a threshold amount of GK activity may be required before a signal sufficient to elicit an effect on PEPPK gene transcription is generated. An alternative explanation is that the two assays used in this experiment have different sensitivities. By this view, the number of cells treated with virus that is required to observe an effect on the dexamethasone/cAMP response is greater than that needed to measure an increase in GK activity. Experiments using an inducible promoter to drive the expression of GK will be needed to distinguish between these two possibilities.

As an additional control, mannoheptulose, an inhibitor of GK enzyme activity (37), was employed to confirm that the glucose effect is the result of GK enzyme activity rather than an artifact of AdCMV-GK-mediated GK protein expression. In the experiment depicted in Fig. 3, 15 mM glucose inhibited hormone-activated PEPPK-CAT gene promoter activity by 70%. Five mM mannoheptulose suppressed the dexamethasone/cAMP response slightly (about 20%) and the same concentration of mannoheptulose blocked the inhibition by glucose. One mM insulin decreased the dexamethasone/cAMP response by 75%, and did so in the absence of glucose. This confirms previous observations which demonstrated that the insulin effect on PEPPK gene promoter activity is independent of glucose (8, 9) (see also Fig. 7 below). Mannoheptulose did not relieve the insulin-mediated inhibition of hormone-stimulated CAT expression in these cells, which demonstrates the specificity of its effect. Together, these data demonstrate that glucose inhibits hormone-activated PEPPK promoter activity in HL1C cells in a GK-dependent manner.
that glucose had no effect on the expression of the PEPCK-CAT fusion gene in untreated HL1C cells, or in HL1C cells treated with AdCMV-β-Gal (Fig. 1). This may be because the endogenous gene in the parental cell line is more sensitive to glucose metabolism than is the PEPCK-CAT fusion gene. Alternatively, the increased glucose may be affecting the stability of mRNA



expression of GK increases the ability of glucose to repress hormone-activated PEPCK gene expression in these cells.

**Time Course and Dose Response of the Glucose Effect—Adenovirus-treated HL1C cells were incubated in the presence or absence of 20 mM glucose for various periods to determine the time course of the glucose effect (Fig. 5). Untreated control cells had only background levels of CAT expression throughout the course of these experiments. However, the dexamethasone/cAMP induction in cells that were treated with AdCMV-GK; in such cells mRNA



expression of GK potentiates the glucose-mediated repression of hormone-activated mRNA



Expression of GK potentiates the glucose-mediated repression of hormone-activated mRNA



Suboptimal Concentrations of Insulin and Glucose Are Additive—HL1C cells were treated with AdCMV-GK, and with dexamethasone/cAMP and various concentrations of insulin in the presence or absence of 5 mM glucose, to test the relationship between glucose and insulin signaling to the PEPCK promoter (Fig. 7). Insulin at 0.01 nM repressed the dexamethasone/cAMP induction of the PEPCK gene significantly, and the maximal effect was reached at 10 nM, a result that is consistent with



FIG. 3. The effect of mannoheptulose on the ability of glucose to repress hormone-activated PEPCK gene promoter activity. HL1C cells were treated with AdCMV-GK and with dexamethasone (Dex)/cAMP. In addition, the cells were treated with the indicated concentrations of mannoheptulose (MH), glucose (Glc), or insulin, in various combinations. After a 12-h incubation in the various agents, the cells were harvested, and CAT activity was determined in the cell lysates. The results are shown as the mean (± S.E., n = 3) of the maximal dexamethasone/cAMP response.

FIG. 4. Expression of GK potentiates the glucose-mediated repression of hormone-activated mRNA

FIG. 5. Time course of the glucose effect on PEPCK gene promoter activity. HL1C cells were exposed to AdCMV-GK and were left untreated (Control) or were treated with dexamethasone (Dex)/cAMP in the presence or absence of 20 mM glucose (Glc) for various times. At the indicated times the cells were harvested, and CAT activity was determined in the cell lysates. The data are presented as the mean (± S.E.) amount of mRNA



Glucose inhibited, in a concentration-dependent manner, the dexamethasone/cAMP-stimulated PEPCK gene promoter activity in HL1C cells treated with AdCMV-GK (Fig. 6). Incubation in 5 mM glucose resulted in a significant decrease of dexamethasone/cAMP-stimulated CAT activity, and 15 mM glucose inhibited the dexamethasone/cAMP response by 80%. The calculated EC



that glucose had no effect on the expression of the PEPCK-CAT fusion gene in untreated HL1C cells, or in HL1C cells treated with AdCMV-β-Gal (Fig. 1). This may be because the endogenous gene in the parental cell line is more sensitive to glucose metabolism than is the PEPCK-CAT fusion gene. Alternatively, the increased glucose may be affecting the stability of mRNA



expression of GK potentiates the glucose-mediated repression of hormone-activated mRNA



Suboptimal Concentrations of Insulin and Glucose Are Additive—HL1C cells were treated with AdCMV-GK, and with dexamethasone/cAMP and various concentrations of insulin in the presence or absence of 5 mM glucose, to test the relationship between glucose and insulin signaling to the PEPCK promoter (Fig. 7). Insulin at 0.01 nM repressed the dexamethasone/cAMP induction of the PEPCK gene significantly, and the maximal effect was reached at 10 nM, a result that is consistent with
Glucose inhibition of PEPCK gene expression

**FIG. 6.** Concentration dependence of the glucose effect on hormone-activated PEPCK gene promoter activity. HL1C cells were treated with AdCMV-GK and with dexamethasone (Dex)/cAMP and the indicated concentrations of glucose for 12 h. The cells were harvested, and CAT activity was determined in the cell lysates. The results are presented as the mean (±S.E., n = 3) of the percent of the maximal dexamethasone/cAMP response determined in the absence of glucose.

**FIG. 7.** The effects of insulin and glucose on hormone-activated PEPCK promoter activity. HL1C cells were treated with AdCMV-GK and with dexamethasone (Dex)/cAMP overnight in the presence of either 5 mM mannitol or 5 mM glucose with the indicated concentrations of insulin. The cells were harvested, and CAT activity was determined in the cell lysates. The results are presented as the mean (±S.E., n = 3) of the percent of the dexamethasone/cAMP response in the presence of 5 mM mannitol. Alternatively, the relative CAT activity was expressed relative to the control data point (no insulin) within each group (inset).

**FIG. 8.** The effects of glucose analogs on PEPCK promoter activity. HL1C cells were treated with AdCMV-GK or were left untreated. The cells were then exposed to dexamethasone (Dex)/cAMP overnight in the presence or absence of 20 mM glucose, 3-O-methylglucose, or 2-deoxyglucose, as indicated. The cells were harvested, and CAT activity was determined in the cell lysates. The results are shown as the mean (±S.E., n ≥ 3) of the maximal dexamethasone/cAMP response (set at 100%).

**DISCUSSION**

This study demonstrates that the glucose-mediated repression of hormone-activated PEPCK gene promoter activity is dependent on the metabolism of glucose. In the liver, glucose enters the cell through the facilitative glucose transporter, GLUT2, and is phosphorylated by GK to generate Glu-6-P, which can then enter a number of metabolic pathways, including glycolysis, glycosylation, and the pentose phosphate pathway (for reviews, see Refs. 2, 15, 16, 20, 38, and 39). In hepatoma cells that do not express GK, such as H4IIE or HL1C cells, the phosphorylation of glucose must be performed by another hexokinase (predominantly hexokinase I). Hexokinase I has a low $K_m$ for glucose (10 μM) and is maximally active well below the glucose concentration in the culture medium. Also, in contrast to GK, hexokinase I is inhibited by physiologic concentrations of Glu-6-P, so that the capacity for glucose phosphorylation is restricted in cells that do not express GK (20, 40). Thus, our results suggest that in cells with a sufficiently high glucose flux, such as those that express GK, glucose generates a signal that regulates the expression of the PEPCK gene.

The importance of GK in liver glucose metabolism is underscored by the fact that overexpression of GK in hepatoma cells or isolated hepatocytes leads to an increase in glycogen deposition and lactate production (35, 41, 42). Conversely, GK expression is undetectable in streptozotocin-induced diabetes (streptozotocin destroys the pancreatic β-cells and so deprives the animal of insulin), a condition that is associated with low glycogen stores, markedly decreased glucose uptake and increased net hepatic glucose output from increased and unrestrained gluconeogenesis (5, 40). Data collected from transgenic animals verifies the important role GK plays in glucose homeostasis. Overexpression of GK in the livers of transgenic mice greatly reduces the hyperglycemia induced by streptozotocin. This is accomplished by a decrease of the mRNAs that encode the gluconeogenic enzymes PEPCK and tyrosine aminotransferase and an increase of the mRNA that encodes pyruvate kinase, a glycolytic enzyme (5). These findings, and the results of the present study, suggest that GK-mediated glucose...
metabolism generates a signal (or signals) that coordinate-ly regulates hepatic genes involved in glucose homeostasis, both positively and negatively, and can do so in the absence of insulin. In this manner glucose participates in the regulation of its own production and utilization.

Glucose analogs have often been used to explore the mechanism(s) by which glucose metabolism affects gene transcription (15, 16, 39). Although useful, these experiments must be interpreted with caution, as these compounds can have several effects. For example, 2-deoxyglucose, which is phosphorylated to 2-deoxyglucose-6-phosphate, mimics the ability of glucose to induce fatty acid synthase and acetyl-CoA carboxylase mRNA in adipocytes and pancreatic beta cells. These experiments, along with many others that show a correlation between Glu-6-P levels and glucose action, form the basis of the hypothesis that Glu-6-P is the metabolite that mediates the glucose response (16). In the present study, we found that 2-deoxyglucose mimics the ability of glucose to repress hormone-activated PEPCK promoter activity, but GK is not needed for this effect (Fig. 8). Cells exposed to 2-deoxyglucose are depleted of ATP (43). Sutherland et al. (44) demonstrated that sodium metarsenate, which inhibits oxidative phosphorylation and therefore results in intracellular ATP depletion, decreases hormone-activated PEPCK promoter activity through a stress-activated pathway (45). Thus it is possible that 2-deoxyglucose represses the PEPCK gene by a mechanism unrelated to its role as a glucose analog. On the other hand, we cannot rule out the possibility that 2-deoxyglucose-6-phosphate, generated by hexokinase, could accumulate to a significant level owing to the fact that it is not readily metabolized. It could then act as an analog of Glu-6-P and affect the activity of the PEPCK gene promoter.

The PEPCK gene promoter consists of a series of hormone response units, each of which is comprised of two or more DNA elements (10, 11, 46, 47). The glucocorticoid response unit is composed of three accessory factor elements, AF1, AF2, and AF3, two glucocorticoid receptor binding sites, and a cAMP response element (10, 48, 49). A mutation in any one accessory factor element (or the CRE) results in a blunted glucocorticoid response element (10, 48, 49). A mutation in any one accessory factor element (or the CRE) results in a blunted glucocorticoid response element (10, 48, 49). A mutation in any one accessory factor element (or the CRE) results in a blunted glucocorticoid response element (10, 48, 49). A mutation in any one accessory factor element (or the CRE) results in a blunted glucocorticoid response element (10, 48, 49).

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