Glucose Stimulates the Activity of the Guanine Nucleotide-exchange Factor eFl-2B in Isolated Rat Islets of Langerhans*

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Over short time periods glucose controls insulin biosynthesis predominantly through effects on preexisting mRNA. However, the mechanisms underlying the translational control of insulin synthesis are unknown. The present study was carried out to determine the effect of glucose on the activity and/or phosphorylation status of eukaryotic initiation and elongation factors in islets. Glucose was found to increase the activity of the guanine nucleotide-exchange factor eFl-2B over a rapid time course (within 15 min) and over the same range of glucose concentrations as those that stimulate insulin synthesis (3–20 mM). A nonmetabolizable analogue of glucose (mannoheptulose), which does not stimulate insulin synthesis, failed to activate eFl-2B.

The best characterized mechanism for modulating eFl-2B activity involves changes in the phosphorylation of the α-subunit of its substrate eFl-2. However, in islets, no change in eFl-2α phosphorylation was seen under conditions where eFl-2B activity was increased, implying that glucose regulates eFl-2B via an alternative pathway.

Glucose also did not affect the phosphorylation states of three other regulatory translation factors. These are the cap-binding factor eFl-4E, eFl-4E-binding protein-1, and elongation factor eFl-2, which do not therefore seem likely to be involved in modulating the translation of the preproinsulin mRNA under these conditions.

Glucose is the major physiological stimulus for insulin biosynthesis in pancreatic β cells with control occurring principally at the level of translation of preformed mRNA (Permutt and Kipnis, 1972; Permutt, 1974; Itoh and Okamoto, 1980; Itoh et al., 1982; Welsh et al., 1986). The mechanism(s) by which elevated concentrations of glucose stimulate insulin biosynthesis is not known, although it is clear that the effect is exerted primarily at the level of peptide chain initiation (Permutt, 1974). The effect is selective for proinsulin synthesis, in that the stimulation of proinsulin synthesis by glucose is proportionally much greater than that of overall protein synthesis (Permutt and Kipnis, 1972).

The translational machinery in eukaryotes is highly complex and involves a number of translation initiation and elongation factors. Changes in the activities of several translation factors are believed to play roles in the regulation of translation in animal cells (Hershey, 1991; Proud, 1992; Redpath and Proud, 1994). Two factors in particular have been studied in detail.

eFl-2 mediates the binding of the initiator Met-tRNA to the 40 S subunit of the ribosome, and changes in its activity are important in regulating translation under a variety of conditions. The best characterized mechanism involves changes in the phosphorylation of its α-subunit at Ser-51. eFl-2(αP) competitively inhibits the factor (eFl-2B) which recycles eFl-2 between successive rounds of initiation (Hershey, 1991; Rowlands et al., 1988a). This recycling process involves the exchange of GDP bound to eFl-2 for GTP by eF-2B, which regenerates active eFl-2-GTP. It plays an important role in the control of translation (Price and Proud, 1994) and the activity of eFl-2B is potentially subject to regulation by a variety of mechanisms including eFl-2α phosphorylation, allosteric control, and phosphorylation of eFl-2B on its largest (ε) subunit. At least three protein kinases have been shown to phosphorylate this polypeptide and evidence has been presented that all three may modulate eFl-2B activity: casein kinases-1 and -2 to activate and glycogen synthase kinase-3 to inhibit (Dholakia and Wahba, 1988; Welsh and Proud, 1993; Denslow et al., 1994; Singh et al., 1994).1

Phosphorylation of eFl-4E, which binds to the 5′-cap of the mRNA, correlates positively with rates of translation, and evidence has been provided that this factor plays a key role in the control of the translation of mRNAs whose 5′-untranslated regions are rich in secondary structure, which impedes mRNA translation (Hershey, 1991; Proud, 1992; Kozak, 1992). eFl-4E is now known to be regulated by an additional mechanism, involving an inhibitory protein (4E-BP1 = eFl-4E binding-protein-1),2 which undergoes phosphorylation in response to certain agents that stimulate translation, and, apparently as a consequence, dissociates from eFl-4E (Pause et al., 1994; Haystead et al., 1994; Lin et al., 1994). This is thought to lead to activation of eFl-4E, perhaps by allowing it to bind to other components of the “cap-binding complex,” which include eFl-4A, a bidirectional RNA helicase.

The elongation step of translation is also subject to regulation, in this case through the phosphorylation of elongation

1 G. I. Welsh and C. G. Proud, unpublished observations.
2 The abbreviations used are: 4E-BP1, eFl-4E-binding protein-1; eFl, eukaryotic elongation factor; eF, eukaryotic initiation factor; PAGE, polyacrylamide gel electrophoresis; MAP, mitogen-activated protein; Tricine, N-[2-hydroxy-1,1-bis(hydroxymethyl)methyl]glycine.
factor-2 (eEF-2). eEF-2 mediates the translocation step of peptide-chain elongation: phosphorylation of eEF-2 by the Ca/calmodulin-dependent eEF-2 kinase causes complete inactivation of eEF-2 (Redpath et al., 1993; Redpath and Proud, 1994).

This work was undertaken to examine the effects of elevated glucose levels on the activity and/or phosphorylation of the regulatory translation factors mentioned above. In this study we show that glucose rapidly activates eEF-2 independently of changes in the phosphorylation of eEF-2, suggesting direct regulation of this factor. Glucose also does not alter the phosphorylation states of eEF-4E or eEF-2 in islets, or the association of 4E-BP1 with eEF-4E.

MATERIALS AND METHODS

Chemicals and Reagents—Chemicals and biochemicals were obtained respectively from BDH (Poole, Dorset, UK) and Sigma (Poole, Dorset, UK) unless otherwise indicated. Radiochemicals and ECL kit were purchased from Amersham International (Amersham Corp., Bucks., UK). Immobilization membrane was from Millipore (Bedford, MA), and ampholytes and m7GTP-Sepharose CL-4B were obtained from Pharmacia Biotech Inc. (Milton Keynes, UK).

Isolation of Rat Islets of Langerhans—Rat islets of Langerhans were isolated by collagenase digestion from 250–300-g male Wistar rats (Marday, 1980) and were prepared in Gey’s and Gey (1936) medium using a modification of the method of Hurst and Morgan (1990). Islets were hand-picked under a dissecting microscope to purge them from exocrine tissue.

For measurement of total protein synthesis, 200 islets were preincubated in 100 μl of Hanks’ balanced salt solution containing 3 or 20 mM glucose for 40 min. This medium was then removed and replaced with 100 μl of Hanks’ balanced salt solution containing 150 μCi of [3H]methionine. Labeling was terminated after 20 min by the addition of ice-cold Hanks’ balanced salt solution. Measurement of counts incorporated into total protein was carried out essentially as described by Guest et al. (1989).

Immunoprecipitation of Insulin—Batches of 200 islets were labeled with [3H]methionine as above following incubation in Hanks’ solution containing 3 or 20 mM glucose for 40 min. Islets were solubilized, and proinsulin was immunoprecipitated using a modification of the method of Guest et al. (1989). Mouse 3B1 antibody was provided by Professor C. N. Hales, Department of Clinical Biochemistry, University of Cambridge, UK. Immunoprecipitates were analyzed by TricineSDS-PAGE followed by fluorography.

Preparation of Islet Extracts—Islets were preincubated at 37°C in Hanks’ balanced salt solution plus 3 mM glucose for the indicated times before experimentation. Groups of islets were then incubated in Hanks medium containing the indicated glucose concentrations. Islets were then washed once in ice-cold phosphate-buffered saline solution and solubilized in buffer A: 70 mM Tris/HCl, pH 7.6, 0.2 mM EDTA, 0.2 mM EGTA, 1 mM diithiothreitol, 100 mM KCl, 10% (v/v) glycerol, 1% Triton X-100, 3 mM microcystin-LR, and protease inhibitors phenylmethylsulfonyl fluoride, pepstatin, and leupeptin.

Assay of eEF-2B Activity—eEF-2B activity was assayed by measuring the exchange of tritiated GDP in preformed eIF-2[3H]GDP complexes for unlabeled GTP as described elsewhere (Mehta et al., 1983; Welsh and Proud, 1992). For these experiments 1000 islets/sample were extracted in 100 μl of buffer A. Incubations (30°C, 20 min) contained 10 μl of cell extract, and formation of complexes was measured by the retention of residual eIF-2[3H]GDP complexes on nitrocellulose filters. eIF-2B activity was assayed by measuring the exchange of tritiated GDP in preformed eIF-2[3H]GDP complexes for unlabeled GTP as described elsewhere (Mehta et al., 1983; Welsh and Proud, 1992). For these experiments 1000 islets/sample were extracted in 100 μl of buffer A. Incubations (30°C, 20 min) contained 10 μl of cell extract, and formation of complexes was measured by the retention of residual eIF-2[3H]GDP complexes on nitrocellulose filters.

Isoelectric Focusing and Immunoblotting—Isolation factors were analyzed by one-dimensional SDS-PAGE and isoelectric focusing, followed by western blotting using both anti-eEF-4E and anti-eEF-4E-BP1 antibodies. Proteins were visualized by enhanced chemiluminescence and quantified by laser densitometry on a phosphorimager.

FIG. 1. Effect of glucose on proinsulin biosynthesis in isolated rat islets of Langerhans. Rat islets of Langerhans were incubated for 20 min in medium containing 3 mM (lane 1) or 20 mM (lane 2) glucose and [35S]methionine. Newly synthesized proinsulin was then immunoprecipitated and analyzed by TricineSDS-PAGE and fluorography. The position of molecular mass markers in kilodaltons is indicated. This result is typical of those obtained from five separate experiments.

Effect of Glucose on Proinsulin Biosynthesis—Initial experiments were performed to demonstrate that the islet preparations were responsive to glucose. As previously demonstrated by others (Permutt and Kipnis, 1972; Guest et al., 1989) glucose elicited a marked effect on proinsulin biosynthesis as measured by the incorporation of [3H]methionine into immunoprecipitable material. Islets incubated in the presence of 20 mM glucose incorporated 2–3 times as much [3H]methionine into total protein as did islets incubated with 3 mM glucose (data not shown). The same conditions resulted in a 20-fold increase in incorporation into proinsulin (Fig. 1).

Regulation of eEF-2B Activity in Islets—eEF-2B activity was measured after treatment of islets for periods of 0–60 min with 20 mM o-glucose. Fig. 2A shows a typical time course for eEF-2B activity with activation evident after 15 min and persisting for at least 60 min. Maximal stimulation was observed between 15 and 30 min with a decrease in activity at 60 min. Over nine entirely separate experiments the activity of eEF-2B after 30 min of treatment with 20 mM glucose averaged 318 ± 109% of the activity in extracts from cells incubated at 3 mM glucose.

The response was assessed over a range of glucose concentrations (3–20 mM o-glucose, 30 min treatment), eEF-2B activity was increased in a dose-dependent fashion (Fig. 2B). This dose response closely matches that reported elsewhere for the effects of varied glucose concentrations on insulin synthesis (Guest et al., 1989).

In a typical experiment where 20 mM glucose resulted in an increase in eEF-2B activity (282% of control where glucose was 3 mM) the hexokinase inhibitor mannoheptulose had no effect on eEF-2B activity in islets on its own (98% of control). However, when used in combination with 20 mM glucose, it suppressed the activation of eEF-2B (151% of control). This is in accordance with the previously reported inhibition by mannoheptulose of the increase in L-type pyruvate kinase mRNA in response to glucose (Marie et al., 1993).

Phosphorylation States of eEF-2α, eEF-4E, and eEF-2—The best known way in which eEF-2B activity can be regulated is via changes in eEF-2α phosphorylation (see Proud 1992). Since a rise in eEF-2B activity was seen here in response to glucose, a fall in eEF-2α phosphorylation would be one way to explain this. In four entirely separate experiments no differences in the level of phosphorylation of eEF-2α were detected when extracts from islets incubated in 3 mM glucose or 20 mM glucose were analyzed by one-dimensional isoelectric focusing (Fig. 3A).

We also analyzed the levels of phosphorylation of eEF-4E and eEF-2 in extracts from cells treated with low or high glucose concentrations.
concentrations. No change was seen in the ratio of unphosphorylated to phosphorylated protein following treatment with 20 mM \( \alpha \)-glucose for eIF-4E (Fig. 3B) or eEF-2 (data not shown). For eIF-4E, densitometric analysis of blots revealed that approximately 50% of protein was in the phosphorylated form in both control and glucose-treated cells.

Association of 4E-BP1 with eIF-4E—eIF-4E was purified from cell extracts on 7-methylGTP-Sepharose and analyzed for the presence of 4E-BP1 by SDS-PAGE followed by immunoblotting. As shown in Fig. 4, the amount of 4E-BP1 detected did not differ between extracts from cells treated with low or high glucose, when compared to the amount of eIF-4E. This indicates that glucose treatment does not cause dissociation of 4E-BP1 from eIF-4E. Species of 4E-BP1 in different states of phosphorylation can be resolved on SDS-PAGE under appropriate conditions (Diggle et al., 1995). Analysis revealed that there was no apparent change in the proportion of 4E-BP-1 in differently migrating species in response to glucose. This indicates that its state of phosphorylation was not altered in response to glucose.

Activities of Glycogen Synthase Kinase-3 and MAP Kinase—Glycogen synthase kinase-3 is implicated in the regulation of eIF-2B (Welsh and Proud, 1993). Since this work showed that raised external glucose leads to activation of eIF-2B, we measured glycogen synthase kinase-3 activity in extracts of islets incubated in the presence of different glucose concentrations. There was no discernable change in glycogen synthase kinase-3 activity in extracts of cells treated with 20 mM glucose as compared to the 3 mM glucose controls (data not shown). MAP kinase may act as an upstream regulator of glycogen synthase kinase-3 and hence, potentially, of eIF-2B (Sutherland et al., 1993; Sutherland and Cohen, 1994; Welsh et al., 1994). As for glycogen synthase kinase-3, the activity of MAP kinase was essentially unchanged on raising the external glucose concentration.

DISCUSSION

In the present study we show that the treatment of islets with glucose results in an increase in eIF-2B activity. This could account for the rise in total protein synthesis observed when islets are exposed to raised external glucose concentrations, since enhanced eIF-2B activity should result in increased supply of Met-tRNA to the ribosome and this is required for the translation of all mRNAs. Modulation of eIF-2B, and thus eIF-2 activity, is important in the overall control of translation under specific conditions such as home deficiency in reticulocytes and

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**Fig. 2.** Effect of glucose on eIF-2B activity in isolated rat islets of Langerhans. Panel A, rat islets of Langerhans incubated in medium containing 20 mM \( \alpha \)-glucose for the indicated periods of time. The data represent the mean of three determinations of eIF-2B activity in a single experiment, where the standard errors were less than 5% for each value. This result is typical of that obtained from five separate time course experiments. For eIF-4E, densitometric analysis of blots revealed that approximately 50% of protein was in the phosphorylated form in both control and glucose-treated cells.

**Fig. 3.** Time courses of the effect of glucose on the phosphorylation of eIF-2, eIF-4E, and eEF-2 (in isolated rat islet cells). Rat islets of Langerhans were incubated in 20 mM \( \alpha \)-glucose for 0 (lane 1), 10 (lane 2), 20 (lane 3), 30 (lane 4), and 60 min (lane 5). Cell extracts were subject one-dimensional isoelectric focusing and Immunoblotted using an anti-eIF-2a (Panel A), anti-eIF-4E (Panel B) antibody. Detection was by enhanced chemiluminescence. The data shown are representative of four individual experiments. Labeled arrowheads indicate the positions of the unphosphorylated and phosphorylated forms of eIF-2a in Panel A and of eIF-4E in Panel B.

**Fig. 4.** Association of eIF-4E with 4E-BP1 in extracts from islets. Islets were incubated in 3 mM \( \alpha \)-glucose (lane 1) or with 20 mM \( \alpha \)-glucose for 15 (lane 2) or 30 min (lane 3), and then extracts were prepared. eIF-4E and associated proteins were isolated by affinity binding to m7GTP-Sepharose and analyzed by SDS-PAGE followed by immunoblotting. Blots were visualized by enhanced chemiluminescence. The positions of eIF-4E and eIF-4EBP1 are marked.

Glycogen synthase kinase-3 is implicated in the regulation of eIF-2B (Welsh and Proud, 1993). Since this work showed that raised external glucose leads to activation of eIF-2B, we measured glycogen synthase kinase-3 activity in extracts of islets incubated in the presence of different glucose concentrations. There was no discernable change in glycogen synthase kinase-3 activity in extracts of cells treated with 20 mM glucose as compared to the 3 mM glucose controls (data not shown). MAP kinase may act as an upstream regulator of glycogen synthase kinase-3 and hence, potentially, of eIF-2B (Sutherland et al., 1993; Sutherland and Cohen, 1994; Welsh et al., 1994). As for glycogen synthase kinase-3, the activity of MAP kinase was essentially unchanged on raising the external glucose concentration.

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3 G. I. Welsh and C. G. Proud, unpublished data.
in the presence of double-stranded RNA in reticulocytes and other cell types. Since the rise in in eF-2B activity was, if anything, larger than the increase in total protein synthesis, components other than eF-2B are presumably limiting. The rise in proinsulin synthesis is much larger than that in total protein synthesis. Lomedico and Saunders (1977) suggested that this might reflect the operation of the “Lodish model.” Lodish (1974) proposed, on the basis of his studies with the mRNAs for the α- and β-chains of hemoglobin, that mRNAs differ in their intrinsic efficiency, such that when the activities of certain components of the translational machinery were limiting, inefficient mRNAs would be translated much less readily than efficient ones. Activation of those limiting components would, of course, lead to an overall stimulation of translation, but would allow especially marked increases in the translation of the inefficient mRNAs. Lomedico and Saunders (1977) postulated that insulin was an example of an inefficient mRNA and might be regulated in this way. Alternatively, there may be a “directed” mechanism operating to secure the increased translation specifically of this mRNA involving specific features of this mRNA or proteins interacting with it.

Although the activity of eF-2B was increased, no change in the level of phosphorylation of eF-2α was seen, indicating that the rise in its activity was not due, as one might have expected, to a decrease in eF-2α phosphorylation. It should also be noted that the assays performed here contain a large excess of “added” substrate eF-2 relative to the endogenous eF-2 in the sample under study: under this condition effects of eF-2(αP) (a competitive inhibitor) (Rowlands et al., 1988a) derived from the extract should be minimized if not eliminated, as discussed previously (Rowlands et al., 1988b; Welsh and Proud, 1992). This suggests that glucose enhances the activity of eF-2B by mechanism distinct from eF-2α phosphorylation. There are now known to be a number of situations where eF-2B activity is altered in intact cells or tissues without any detectable change in eF-2α phosphorylation (Kimball and Jefferson, 1988; Rowlands et al., 1988b; Jeffery et al., 1990; Welsh and Proud, 1992).

In the absence of a change in eF-2α phosphorylation, how can the changes in eF-2B activity be brought about? It is likely that they involve direct regulation of eF-2B itself, and this might in principle be a consequence of either allosteric regulation or of covalent modification. Several agents, such as nicotinamide adenine dinucleotides and polyamines, modulate eF-2B activity allosterically in vitro (Dholakia et al., 1986; Gross et al., 1988; Gross and Rubino, 1989; Oldfield and Proud, 1992; Singh et al., 1994; Kimball and Jefferson, 1995). However, it is not clear whether the concentrations of these compounds present in vivo (or changes in their concentration following cell stimulation) are in the range required to modulate eF-2B activity. Furthermore, the assays performed in this and the other studies cited above entailed extensive dilution of the samples relative to the intracellular milieu, and these low affinity ligands are likely to be diluted out beyond the level at which they exert their allosteric effects. Another possible mechanism is the phosphorylation of eF-2B itself. It is phosphorylated in vitro by at least three protein kinases (casein kinases-1 and -2 and glycosynthesine kinase-3), phosphorylation by each of which may modulate the exchange activity of eF-2B (Dholakia and Wahba, 1988; Welsh and Proud, 1993; Denslow et al., 1994). Phosphorylation by glycosynthesine kinase-3 appears to inhibit the activity of eF-2B, while the other two are reported to activate. However, it is not clear whether the activities of the casein kinases are altered following glucose stimulation of islets and in our hands neither of these kinases has any measurable affect on eF-2B activity (Oldfield and Proud, 1992). In the present work we found that glycosynthase kinase-3 activity and the activity of MAP kinase, a potential upstream regulator of glycosynthase kinase-3 (Sutherland et al., 1993; Cross et al., 1994; Sutherland and Cohen, 1994; Welsh et al., 1994), were not altered under conditions of elevated external glucose. Thus it is unclear how the changes in the level of eF-2B activity are brought about.

Other translation factors are also believed to play key roles in the control of translation, especially those interacting with mRNA, which may modulate translation in a selective manner (Manzella et al., 1991; Rhoads, 1993; Sonenberg, 1993). Two such factors are eF-4E and 4E-BP1, which are most likely to control the translation of mRNAs whose 5′-untranslated regions are rich in secondary structure. However, no changes in the phosphorylation states of either protein, or in their association with one another, were observed in these studies. They do not therefore appear likely to be important in the regulation of proinsulin synthesis in response to glucose. Although the 5′-untranslated region of the proinsulin mRNA does contain potential stem loops, these are relatively small (∆G = −8 to −13 kcal/mol depending on species; see Knight and Docherty (1992)) compared to those known to significantly influence translational efficiency (Kozak, 1989, 1991; Pellietier and Sonenberg, 1985). Thus is unlikely that these potential secondary structure elements play a role in controlling proinsulin synthesis, and it is thus unsurprising that eF-4E and 4E-BP1 seem not to be involved in this process. The lack of change in the phosphorylation of eF-2 also eliminates this protein as being involved in the glucose-induced regulation of proinsulin translation.

In conclusion, it seems possible that the enhancement of eF-2B activity contributes to the activation of proinsulin mRNA translation caused by glucose although other mechanisms may also be involved. These include the proteins recently identified as binding to the 5′-untranslated region of this mRNA (Knight and Docherty, 1992). An important finding of these studies is that glucose activates the exchange factor eF-2B independently of changes in eF-2α phosphorylation.

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