Glucose Regulates Islet Amyloid Polypeptide Gene Transcription in a PDX1- and Calcium-dependent Manner*

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Islet amyloid polypeptide (IAPP) and insulin are expressed in the β-cells of the islets of Langerhans. They are co-secreted in response to changes in glucose concentration, and their mRNA levels are also regulated by glucose. The promoters of both genes share similar cis-acting sequence elements, and both bind the homeodomain transcription factor PDX1, which plays an important role in the regulation of the insulin promoter and insulin mRNA levels by glucose. Here we examine the role of PDX1 in the regulation of the human IAPP promoter by glucose. The experiments were facilitated by the availability of a human β-cell line (NES2Y) that lacks PDX1. NES2Y cells also lack operational KATP channels, resulting in a loss of control of calcium signaling. We have previously used these cells to show that glucose regulation of the insulin gene is dependent on PDX1, but not calcium. In the mouse β-cell line Min6, glucose (16 mM) stimulated a 3.5-4-fold increase in the activity of a −222 to +450 IAPP promoter construct compared with values observed in 0.5 mM glucose. In NES2Y cells, glucose failed to stimulate transcriptional activation of the IAPP promoter. Overexpression of PDX1 in NES2Y cells failed to reinstate glucose-responsive control of the IAPP promoter. Glucose effects on the IAPP promoter were observed only in the presence of PDX1 when normal calcium signaling was restored by overexpression of the two KATP channel subunits SUR1 and Kir6.2. The importance of calcium was further emphasized by an experiment in which glucose-stimulated IAPP promoter activity was inhibited by the calcium channel blocker verapamil (50 μM). Verapamil was further shown to inhibit the stimulatory effect of glucose on IAPP mRNA levels. These results demonstrate that like the insulin promoter, glucose regulation of the IAPP promoter is dependent on the activity of PDX1, but unlike the insulin promoter, it additionally requires the activity of another, as yet uncharacterized factor(s), the activity of which is calcium-dependent.

IAPP is a 37-amino acid peptide of the calcitonin gene family (1). IAPP was originally isolated from amyloid deposits in islets of Langerhans from non-insulin-dependent diabetic pancreas and insulinomas (2, 3). It has since been shown to play a role in the normal regulation of glucose metabolism (4, 5). IAPP and insulin are co-secreted in a regulated manner following stimulation with glucose and a variety of other secretagogues (6, 7). Transcription of the IAPP (8, 9) and insulin (10) genes is also stimulated by glucose. In the case of insulin, multiple cis-acting elements located within a relatively short region (−1 to −360) upstream of the start site contribute to the regulation of the gene by glucose and other nutrients (11). The importance of calcium was further emphasized by an experiment in which glucose-stimulated IAPP promoter activity was inhibited by the calcium channel blocker verapamil (50 μM). Verapamil was further shown to inhibit the stimulatory effect of glucose on IAPP mRNA levels. These results demonstrate that like the insulin promoter, glucose regulation of the IAPP promoter is dependent on the activity of PDX1, but unlike the insulin promoter, it additionally requires the activity of another, as yet uncharacterized factor(s), the activity of which is calcium-dependent.

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1 The abbreviations used are: IAPP, islet amyloid polypeptide; CAT, chloramphenicol acetyltransferase.
Glucose Regulates IAPP Gene Transcription

EXPERIMENTAL PROCEDURES

Cell Culture—NES2Y cells were derived from islets of Langerhans isolated from the pancreas of a patient with persistent hyperinsulinemic hypoglycemia of infancy as described previously (21). Isolated intact human islets were prepared and maintained as described previously (24). Min6 cells, a β-cell line derived from transgenic mice expressing the SV40 large T antigen under the control of the rat insulin promoter (25), were cultured in Dulbecco’s modified Eagle’s medium containing 5 or 25 mM glucose and supplemented with 15% heat-inactivated myocyte fetal calf serum (Sigma) and 2 mM t-glutamine.

Plasmids—IAPP gene promoter plasmids pTKCAT, pTAC138, pTAC222, and pTAC2798, pTAC477, pTAC391, pTAC2798, and pTAC138 were constructed according to the manufacturer’s protocols. Where appropriate, plasmids were derived by stable transfection of NES2Y cells: NES-PDX1 cells overexpress PDX1; NESK cells overexpress SUR1 and Kir6.2; and NISK9 cells overexpress PDX1, SUR1, and Kir6.2. Overexpression of the appropriate transgenes was confirmed by Northern blotting, Western blotting, and analysis of ion channel activity as described previously (23, 26). Transient CAT reporter gene assays were performed using the Quant-T-CAT assay system (Amersham Pharmacia Biotech, Buckinghamshire, United Kingdom) according to the manufacturer’s protocols. Where appropriate, cells were incubated in the presence of 50 μM verapamil for 30 min prior to stimulation with 20 mM glucose. Samples were equalized for protein content as measured by the standard Bradford assay.

RNA Extraction and Northern Blot Analysis—Total RNA was prepared from Min6 cells using the Trizol reagent (Life Technologies, Inc.) according to the manufacturer’s protocol. Northern blot analysis was performed as described previously (23) using, as probe, a full-length human IAPP cDNA (a kind gift from Dr. A. Clark, University of Oxford, Oxford, United Kingdom) and a human insulin cDNA. Specific hybridization was then detected and quantified by direct imaging using the Packard InstantImager.

Immunocytochemistry—The anti-PDX1 antibody was from Dr. C. V. E. Wright (Vanderbilt University), and the anti-IAPP antibody was from Dr. A. Clark. The monoclonal anti-insulin antibody (3B1) was from Professor C. N. Hales (University of Cambridge); the anti-GLUT2 antibody was from BioGenosys; the anti-glucokinase antibody was from Dr. S. Lenzen (University of Hannover); and the anti-PC3 and anti-PC2 antibodies were from Dr. D. F. Steiner (University of Chicago). NES2Y cells were grown on 8-chamber slides to 50% confluence, washed four times in phosphate-buffered saline, and fixed in ice-cold methanol for 10 min at 4 °C. Cells were then incubated for 15 min at room temperature in blocking buffer containing 0.7% (v/v) glycerol, 0.2% (v/v) Tween 20, and 2% (w/v) bovine serum albumin. Primary antibodies were added to each chamber in blocking buffer, and the samples were left overnight at 4 °C. Following four washes in blocking buffer, secondary antibody was added to each well at 1:400 dilution in blocking buffer. The samples were then gently rocked for 60 min in the dark at room temperature. Finally, cells were washed in 0.4% Tween 20, 0.7% glycerol, and 2% bovine serum albumin for 1–2 h with gentle rotation at room temperature in the dark before mounting medium containing 4,6-diamidino-2-phenylindole staining (blue) indicates the nucleus. Controls with anti-primary antibody alone, anti-secondary antibody alone, or nonimmune mouse or rabbit serum all produced no staining. Magnification is ×200.

RESULTS

NES2Y is a proliferating human β-cell line derived from a patient with persistent hyperinsulinemic hypoglycemia of infancy (20). In keeping with the clinical features of this disease, i.e. profound hypoglycemia due to inappropriate hypersecretion of insulin, NES2Y cells secrete high levels of insulin and are unresponsive to glucose. The cells exhibit a loss of KATP channel activity, with a resultant loss of [Ca2+]I regulation. In addition, expression of PDX1 is impaired, leading to a loss of glucose-responsive insulin gene transcription (21, 23). A normal insulin secretory response to changes in glucose concentrations within the physiological range can be achieved by stably transfecting NES2Y cells with cDNAs encoding SUR1, Kir6.2, and PDX1 (26). In the current experiments, NES2Y cells were used between passages 14 and 20. Under these conditions, the cells secreted insulin (11.13 ng/10⁶ cells/24 h) and, in addition to insulin, showed normal expression of IAPP, PC2, PC3, GLUT2, and glucokinase as measured by immunocytochemistry (Fig. 1). The cells did not express glucagon (data not shown) or PDX1 (Fig. 1).

In preliminary experiments, we were able to confirm (27) by Northern blot analysis that IAPP mRNA levels were increased in human islets of Langerhans incubated in 20 versus 3 mM glucose (data not shown). We next investigated the effect of

Fig. 1. Expression of phenotypic markers in NES2Y cells. NES2Y cells were subjected to immunocytochemistry using specific anti-insulin, anti-IAPP, anti-glucokinase, anti-GLUT2, anti-PC2, anti-PC3, and anti-PDX1 antibodies. The primary antibody was coupled to tetramethylrhodamine B isothiocyanate-conjugated (red) or fluorescein isothiocyanate-conjugated (green) second antibody. In each panel, 4,6-diamidino-2-phenylindole staining (blue) indicates the nucleus. Controls with anti-primary antibody alone, anti-secondary antibody alone, or nonimmune mouse or rabbit serum all produced no staining. Magnification is ×200.
glucose on the IAPP promoter in Min6 and NES2Y cells. The human IAPP promoter is complex, being regulated by sequences both upstream and downstream of the transcriptional start site (19). Reporter gene analysis was performed in the mouse β-cell line Min6 using a series of constructs containing regions −2798 to +450 (pTAC−2798), −477 to +450 (pTAC−477), −391 to +450 (pTAC−391), −222 to +450 (pTAC−222), and −133 to +450 (pTAC−133) of the human IAPP promoter (Fig. 2). These analyses confirmed the findings of Carty et al. (19), who identified a “minimal control region” of the human IAPP promoter, spanning sequences from −222 to +450 base pairs relative to the transcriptional start site.

To investigate whether this minimal control region of the human IAPP promoter was responsive to glucose, the pTAC−222 construct was transfected into Min6 cells (Fig. 3A), which were then incubated in 0.5 or 16 mM glucose. In Min6 cells, the pTAC−222 construct gave a 3.5–4-fold increase in transcriptional activity in high glucose compared with low glucose concentrations. No significant effect of glucose was observed on the control construct pTKCAT. In NES2Y cells (Fig. 3B), no effect of glucose was observed on either construct. These results are reminiscent of those observed for the insulin promoter, which was responsive to glucose in Min6 cells, but not in NES2Y cells (23).

To determine whether, as for the insulin promoter (23), PDX1 was essential for the glucose effects on the human IAPP minimal promoter, pTAC−222 was transfected into NES-PDX1 cells. NES-PDX1 cells contain the signaling pathway necessary for activation of PDX1. Thus, in low glucose, PDX1 is localized around the perimeter of the nucleus as described previously (28, 29). When NES-PDX1 cells were incubated in high glucose, PDX1 was activated as judged by electrophoretic mobility shift assay (data not shown) and became localized within the nucleus (Fig. 4). Surprisingly, there was no effect of glucose on the pTAC−222 construct in NES-PDX1 cells (Fig. 5A). Like the parental NES2Y cell line, NES-PDX1 cells exhibit impaired voltage-dependent Ca2+ influx (23). To determine whether changes in [Ca2+]i might be important in regulating the human IAPP promoter, we generated a cell line (NESK) in which NES2Y cells were stably transfected with the two components

![FIG. 2. Deletion analysis of the IAPP promoter.](image)

![FIG. 3. Effect of glucose on the IAPP promoter in Min6 and NES2Y cells.](image)

![FIG. 4. Regulation of PDX1 in NES-PDX1 cells.](image)
of the K<sub>ATP</sub> channel, i.e. SUR1 and Kir6.2. Overexpression of SUR1 and Kir6.2 in the NESK cell line has previously been shown to restore normal K<sub>ATP</sub> channel activity, normal glucose regulation of [Ca<sup>2+</sup>], and normal glucose-regulated insulin secretion (26). Glucose had no effect on the human IAPP promoter activity or on the control construct (pTKCAT) in NESK cells (Fig. 5B).

We next examined the activity of the human IAPP promoter in the NISK9 cell line, in which NES2Y cells were stably transfected with the three transgenes, i.e. PDX1, SUR1, and Kir6.2. These cells have normal K<sub>ATP</sub> channel activity and modulate voltage-dependent [Ca<sup>2+</sup>] signals in response to glucose (26). NISK9 cells showed a pattern of human IAPP promoter activity similar to that observed in Min6 cells, with 20 mM glucose promoting a 3.5–4-fold increase in pTAC<sup>-222</sup> transcriptional activity compared with that observed in 3 mM glucose activity (Fig. 5C). These results demonstrate that regulation of the human IAPP promoter by glucose is dependent on PDX1, but additionally requires normal glucose elevation of [Ca<sup>2+</sup>]i.

To confirm that changes in [Ca<sup>2+</sup>]i were required for glucose regulation of the human IAPP promoter, glucose stimulation of NISK9 and Min6 cells was performed in the presence of the calcium channel blocker verapamil. In both NISK9 and Min6 cells, glucose elicited a 3.5–4-fold increase in pTAC<sup>-222</sup> transcriptional activity, which was inhibited by the addition of 50 μM verapamil (Fig. 6). Neither glucose nor verapamil had any effect on the control construct (pTKCAT) or pTAC<sup>-222</sup> construct, which contains the −222 to +450 region of the human IAPP gene promoter, as indicated. Transfected cells were incubated for 3 h in 0.5 mM (white bars) or 16 mM (black bars) glucose. Values are shown as relative CAT activity standardized against protein content, expressed as -fold increase over basal levels. Values represent the mean ± S.D. from six replicates. Each set of values has been reproduced in three separate experiments.

**DISCUSSION**

There is evidence that the IAPP and insulin genes are coordinately regulated, as seen, for example, in the response to hypoglycemia and fasting in the rat (8). However, other studies have shown that the levels of each hormone can be regulated independently. For example, in chronic streptozotocin diabetes in rats, IAPP mRNA levels, as measured by quantitative in situ hybridization, were increased or unaffected by low and high doses of streptozotocin, whereas insulin mRNA levels were unaffected or reduced (30). Furthermore, administration of dexamethasone to low dose streptozotocin-treated rats resulted in an increase in IAPP mRNA levels, whereas insulin mRNA levels were markedly reduced (30). Insulin and IAPP gene expression was also shown to be uncoupled in pluripotent rat tumor cell lines under certain culture conditions and following passage in vivo (31). In human islets of Langerhans, following treatment with high glucose for relatively long periods, there was a greater stimulation of IAPP than insulin mRNA levels (27). Taken together, these findings that insulin and IAPP mRNA levels are regulated separately are therefore compatible with the results reported in the present study demonstrating that the regulation of the IAPP and insulin promoters by glucose involved different mechanisms. Both are dependent on PDX1, but whereas the effects of glucose on the insulin promoter are independent of changes in [Ca<sup>2+</sup>], (23), the effects on the IAPP promoter are calcium-dependent. We also show that this difference in calcium dependence can also be seen at the level of glucose effects on insulin and IAPP mRNAs. This latter
Effect on IAPP mRNA levels is consistent with the previous findings of Gasa et al. (32).

Regulation of IAPP gene expression is dependent on a large and complex promoter region, the activity of which is modulated by sequence elements lying both upstream and downstream of the transcriptional start site (19). The critical promoter sequences for transcriptional activation lie between -222 and +450 relative to the transcriptional start site. The intronic region from +104 to +434 base pairs appears to be important in post-transcriptional regulation of IAPP expression (19), whereas the promoter proximal region between -222 and -91 base pairs holds the key to the transcriptional regulation of the IAPP gene. This region contains three A-box DNA-binding motifs (CTAATG), which occur at positions -83 (A1), -144 (A2), and -202 (A3) relative to the transcriptional start site. A-boxes occur at similar sites in the insulin promoter, where they have been shown to bind the homeodomain transcription factor PDX1. The A2 site in the IAPP promoter, which has been the best characterized, also binds PDX1 (18, 19). However, Wang and Drucker (33) have shown that the LIM homeodomain transcription factor Isl1, which, like PDX1 (34), plays a role in development of the pancreas (35), may also bind at the A2 site. Isl1 does not function in the regulation of the insulin promoter, although it does activate the IAPP promoter (33). It is possible that Isl1, although not restricted to β-cells, may be the additional calcium-dependent factor involved along with PDX1 in mediating the effects of glucose on the IAPP gene.

Differences in the transcriptional regulation of the human insulin and IAPP genes may be of strategic therapeutic value. It has been proposed that overexpression of IAPP contributes to the development of non-insulin-dependent diabetes (36), a view supported by transgenic mouse studies involving the overexpression of human IAPP in islets of Langerhans (37–40). Thus, inhibiting IAPP transcription could be a valuable therapeutic option in the treatment of non-insulin-dependent diabetes. Targeting PDX1 by using inhibitors such as SB203580 or LY294002, directed at the cell signaling pathway involved in its activation (16), would certainly affect IAPP expression, but would also affect expression of the insulin gene. A better strategy would be to target factors involved in IAPP gene expression that are not essential for expression of other β-cell-specific genes. The present study, by demonstrating significant differences in the regulation of the insulin and IAPP genes, suggests that such IAPP-specific factors (possibly Isl1) exist and remain to be identified.

In conclusion, the present study has established that critical differences exist between the regulation of the human insulin and IAPP promoters. Although sharing many common sequence elements, glucose regulation of each promoter has distinguishable requirements. Previous studies have established that regulation of the human insulin gene promoter is dependent on the activity of PDX1, but occurs entirely independently of any changes in [Ca^{2+}]_{i} (23). We have now shown that glucose regulation of IAPP gene transcription is also dependent on the activity of PDX1. However, IAPP gene transcription additionally requires the activity of another transcription factor(s), the activity of which appears to be dependent on glucose-induced Ca^{2+} influx into the pancreatic β-cell.

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