The hormone glucose-dependent insulinotropic polypeptide (GIP) is an important regulator of insulin secretion. GIP has been shown to increase adenyl cyclase activity, elevate intracellular Ca\(^{2+}\) levels, and stimulate a mitogen-activated protein kinase pathway in the pancreatic \(\beta\)-cell. In the current study we demonstrate a role for arachidonic acid in GIP-mediated signal transduction. Static incubations revealed that both GIP (100 nM) and ATP (5 mM) significantly increased \([^{3}H]Ara\)c and stimulating \([^{3}H]AA\) release. Our data suggest that GIP is the proximal signaling intermediate responsible for GIP-stimulated AA release. Finally, stimulation of GIP-mediated AA production was shown to be mediated via a Ca\(^{2+}\)-dependent phospholipase A\(_2\). Arachidonic acid is therefore a new component of GIP-mediated signal transduction in the \(\beta\)-cell.

Glucose-dependent insulintropic polypeptide (GIP, or gastric inhibitory polypeptide)\(^1\) is a 42-amino acid polypeptide hormone synthesized by mucosal K cells of the duodenum and jejunum and released into the circulation in response to nutrient ingestion (1–4). GIP and glucagon-like peptide-1 (GLP-1) are thought to be the major hormones (incretins) that constitute the endocrine component of the enteroinsular axis in humans and are responsible for at least 50% of postprandial insulin secretion (5). In non-insulin-dependent diabetes mellitus (type 2 diabetes mellitus), the incretin effect following oral glucose administration is reduced or absent (6, 7), and the ability of intravenous GIP, but not GLP-1, to stimulate insulin secretion is severely blunted (7, 8). This implies that a defective GIP signal transduction system and/or a reduced number of functional GIP receptors may contribute to the pathophysiology of type 2 diabetes. A greater understanding of the signal transduction systems activated by GIP should assist in determining whether reduced responsiveness involves changes at this level.

The receptor for GIP (9–11) is a member of the class II G protein-coupled receptor superfamily, which includes receptors for glucagon, GLP-1, secretin, and vasoactive intestinal polypeptide (12). Stimulation of the GIP receptor has been shown to stimulate adenyl cyclase and elevate intracellular cAMP levels in pancreatic islets (13), islet tumor cell lines (14), and various cell lines transfected with the GIP receptor (10, 15, 16). In addition, GIP has been shown to increase uptake of Ca\(^{2+}\) into isolated islets (17) and increase intracellular Ca\(^{2+}\) levels in HIT-T15 (18), RINm5F (9), and COS cells (10). We have shown that the GIP receptor probably couples to various Ca\(^{2+}\) channels (10), but there is no evidence for GIP-stimulated IP\(_3\) production (18). There is, however, evidence that GIP stimulates insulin secretion (19) and activation of mitogen-activated protein kinase (20) via a wortmannin-sensitive pathway, implying a role for phosphatidylinositol 3-kinase. It is therefore clear that GIP action on the pancreatic \(\beta\)-cell involves several interacting signal transduction pathways.

Phospholipase A\(_2\) (PLA\(_2\)) catalyzes the hydrolysis of the sn-2 fatty acid substituents from glycerophospholipid substrates to yield a free fatty acid and a 2-lysoosphospholipid (21, 22). In the \(\beta\)-cell, glucose has been shown to hydrolyze membrane phospholipids, leading to the accumulation of arachidonic acid (AA), which ultimately amplifies insulin secretion (23, 24). PLA\(_2\) has been identified in both human and rat islets (25), as well as in various insulinoma cell lines (26, 27). These \(\beta\)-cell models have been shown to express Ca\(^{2+}\)-dependent cytosolic PLA\(_2\) (28), ATP-stimulatable Ca\(^{2+}\)-independent cytosolic PLA\(_2\) (iPLA\(_2\)), and secretory PLA\(_2\) (sPLA\(_2\)) isoforms. A role for all of these enzymes in glucose-induced insulin release has been suggested (25, 26, 30–32).

Heterotrimeric G proteins are activated by G protein-coupled receptors and undergo GDP/GTP exchange at the level of the \(\alpha\) subunit, leading to dissociation of the trimer into \(\alpha\) and \(\beta\gamma\) subunits (33). The \(\beta\gamma\) subunits have recently been shown to act on a number of effector targets including ion channels,
Role for Arachidonic Acid in GIP-mediated Insulin Secretion

These observations provided the rationale for determining whether arachidonic acid and PLα₂ are involved in the glucose potentiating effects of GIP in the β-cell, with a focus on Gβγ subunits as a coupling mechanism. We show for the first time that GIP stimulates AA release from CHO-K1 cells and clonal β-cells (βTC-3). Coupling of the GIP receptor to AA production in CHO-K1 cells was via Gβγ subunits, whereas Ca²⁺ was shown to be the mediator in βTC-3 cells. The PLα₂ isoform activated by GIP in βTC-3 cells was Ca²⁺-independent and hypothesized to be the same as that activated by glucose when stimulating insulin secretion.

EXPERIMENTAL PROCEDURES

Cell Transfection and Tissue Culture—CHO-K1 cells cultured in Dulbecco’s modified Eagle’s medium/Ham’s F-12 medium (Life Technologies, Inc.) and supplemented with 10% newborn calf serum (Cansera, Rexdale, Canada) were stably transfected with the wild type rat GIP receptor as described previously (10, 15). The CHO-K1 cell line obtained by pooling clones was termed rGIP-15 and has previously been shown to express receptors at levels similar to high level expressing clones (15). In experiments targeted at investigating a role for Gβγ signaling, rGIP-15 clones were transiently transfected with plasmid DNA encoding the C terminus of β-adrenergic receptor kinase (βARKct) or the empty vector (pRK5). Briefly, 40–60% confluent monolayers in 10-cm culture plates (Becton Dickenson, Lincoln Park, NJ) were transfected using Superfect™ (Qiagen, Valencia, CA) transfection reagent according to the manufacturers’ protocol. Cells were harvested 18–24 h post-transfection and passed into 24-well plates for subsequent arachidonic acid release experiments. The empty plasmid pRK5 and the plasmid pRK-βARKct (495–689) were kindly provided by Dr. R. J. Lefkowitz (37). Passages 20–30 of rGIP-15 cells were used in these experiments.

βTC-3 cells were obtained from a frozen stock that was originally a gift from Dr. S. Efrat (Diabetes Center, Albert Einstein College of Medicine, New York) (38). Cells were cultured in low glucose (5.5 mM) Dulbecco’s modified Eagle’s medium (Life Technologies, Inc.) supplemented with 12.5% horse serum (Cansera) and 2.5% fetal bovine serum (Cansera). Passage and 30–32 were used in these experiments.

Iodination of GIP and Binding Analysis—Synthetic porcine GIP (5 μg) was iodinated by the chloramine-T method, and the 125I-GIP was further purified by reverse phase high performance liquid chromatography to a specific activity of 250–300 μCi/μg (10). The aliquots were subsequently lyophilized and stored at −20 °C until use. Competitive binding analyses were performed as described previously with minor modifications (10). Briefly, CHO-K1 cells plated 2 days prior in 24-well plates were washed twice with 4 °C Krebs-Ringer (115 mM NaCl, 4.7 mM KCl, 1.2 mM KH₂PO₄, 10 mM NaHCO₃, 1.28 mM CaCl₂, 1.2 mM MgSO₄) containing 10 mM HEPES and 0.1% bovine serum albumin, pH 7.4 (KRBH), and incubated in triplicate for 14–18 h at 4 °C with 125I-GIP (50 000 cpm/well) in the presence or the absence of unlabeled GIP (synthetic human GIP₁₆₉–₁₇₇, Bachem, Torrance, CA). After two consecutive washes in ice-cold buffer, cells were solubilized with 0.1 M NaOH and transferred to test tubes for counting. Nonspecific binding was defined as that measured in the presence of an excess of human GIP (1 μM), and specific binding was expressed as a percentage of maximum binding (%BB). cAMP and Insulin Determination—The cells were passaged into 24-well culture plates at 5 × 10⁴ cells/well for CHO-K1 clones and 5 × 10⁵ cells/well for βTC-3 cells. For cAMP studies, cells were washed twice with KRBH and then stimulated for 30 min with GIP in the presence of the phosphodiesterase inhibitor 3-isobutyl-1-methylxanthine at 0.5 mM concentration (RBI/Sigma). Following stimulation, reactions were stopped, and cells were lysed in 70% ice-cold ethanol, cellular debris was removed by centrifugation, and cAMP was subsequently quantified by radioimmunoassay (Biomedical Technologies Inc., Stoughton, MA).

Arachidonic Acid Release—Arachidonic acid release was determined by methods adapted from Shuttleworth and Thompson (40). Cells were harvested and passaged into 24-well culture plates at 8 × 10⁵ cells/well for CHO-K1 clones and 2 × 10⁶ cells/well for βTC-3 cells. The respective media were replaced with media containing 0.125 μCi/ml [³H]AA (PerkinElmer Life Sciences) 18–24 h following passaging, and the plates were incubated for an additional 36–48 h. Prior to the addition of enzymes, and kinases (33). Recent data suggested that inactivation of free Gβγ completely abolished KCl, Ca²⁺, and GTPγS-evoked insulin release from HIT-T15 cells (34), establishing a role for these subunits in insulin secretion. A role for Gβγ has also been demonstrated in the coupling of PLα₂ and arachidonic acid production in rod outer segments (35) and to the activation of cardiac potassium channels (36).
of experimental agents, the wells were washed twice with 0.5 ml of KRBH and allowed to equilibrate for 1 h. Ca\(^{2+}\)-free experiments were conducted in KRBH containing equimolar Mg\(^{2+}\) and supplemented with 10 mM EGTA. The agonists were dissolved in Krebs-Ringer buffer, added in triplicate (0.5 ml total volume/well), and incubated for the length of time shown in the figure legends. As a positive control, ATP was added at a final concentration of 5 mM. When used, the inhibitor haloenol lactone suicide substrate (HELSS; Calbiochem, La Jolla, CA) was added for 30 min prior to washing and addition of agonists. After incubation, 0.4-ml aliquots were placed into scintillation vials followed by the addition of 10 ml of Econo 2 scintillation fluid (Fisher), and the radioactivity was determined by liquid scintillation spectrometry. AA released from cells was generally between 2–6% of total [3H]AA incorporated into cells.

**Data Analysis**—The data are expressed as the means \pm S.E. with the number of individual experiments presented in the figure legend. All of the data were analyzed using the nonlinear regression analysis program PRISM (Graphpad, San Diego, CA), and the significance was tested using the Student’s \(t\) test and analysis of variance (ANOVA) with the Tukey post-test \((p < 0.05)\) as indicated in figure legends.

**RESULTS**

Initial studies were targeted at investigating GIP receptor signaling in an expression system, the rGIP-15 clone of CHO-K1 cells. Static incubations (45 min) revealed a concentration dependence to GIP-stimulated arachidonic acid production (Fig. 1a). In agreement with previous, non-incretin, studies on CHO-K1 cells (41, 42), ATP (5 mM) increased AA release from rGIP-15 cells by greater than 200% \((p < 0.01, n = 4)\). Parallel studies were performed in \(\beta\)TC-3 cells, a model of the pancreatic \(\beta\)-cell. These cells respond to arachidonic acid in a glucose-dependent manner (Fig. 2). In the presence of glucose, AA potentiated insulin secretion at concentrations as low as 10 \(\mu\)M (Fig. 2a), whereas 20-fold greater concentrations were required before a response was observed under glucose-free conditions (Fig. 2b). The potentiation of insulin secretion elicited by 100 \(\mu\)M AA is comparable with that elicited by 100 nM GIP under 11 mM glucose conditions (Fig. 2a versus Fig. 8). GIP was found to stimulate AA release in a concentration-dependent manner (Fig. 1, b and c). Interestingly, the EC\(_{50}\) value for GIP-stimulated AA release (1.4 nM \pm 0.62 nM; \(n = 3\)) was similar to that for insulin secretion in these cells (data not shown), in contrast to the 5-fold higher EC\(_{50}\) value for cAMP production (39).
cellular glucose (Fig. 1c), indicating that GIP-induced and glucose-induced increases in AA release were mediated via separate pathways.

Analysis of the time dependence of AA release in rGIP-15 cells demonstrated maximal release at 10 min (Fig. 3a), which correlates well with that for GIP-stimulated cAMP production (maximal plateau reached at 10–15 min in rGIP-15 and βT3-3 cells; n = 3). In contrast, GIP-induced AA release was not detected before 30 min of incubation in the βT3-3 cells (Fig. 3b), and glucose-induced release was not observed until after 60 min of incubation (Fig. 3b). It was considered possible that these differences in onset of response may reflect alternative rate pathways.

Because Gβγ has been previously implicated in the activation of phospholipase A2 (35), an inhibitor peptide of Gβγ (35), and glucose-induced increases in AA release were mediated via separate pathways. An inhibition of receptor internalization was monitored because Gβγ subunits have been shown to be required for G protein receptor kinase-mediated G protein-coupled receptor internalization (43). Expression of βARKct was associated with an inhibition of receptor internalization in these cells (versus pRK5 vector control; n = 3). Initial experiments were conducted to examine GIP receptor binding and cAMP production in this expression model. βARKct expression was not found to have any significant effect on either receptor affinity for GIP or on activation of adenylyl cyclase (IC50 values for binding: 3.95 nM ± 0.91 (n = 3) and 4.07 nM ± 0.97 (n = 3); EC50 values for cAMP production: 0.73 nM ± 0.12 (n = 3) and 0.49 nM ± 0.09 (n = 3) for vector and βARKct, respectively). GIP receptors were shown, for the first time, to be capable of functionally coupling to AA production through Gβγ dimers, because the expression of βARKct significantly suppressed the GIP-mediated response by almost 70% (Fig. 4, p < 0.05). Purinergic receptors were also found to be coupled to AA production through Gβγ dimers, because βARKct expression reduced ATP-stimulated AA production by greater than 40%.

To characterize further the pathway by which AA is produced in the βT3C-cell by GIP, the effect of βARKct expression was investigated. To ensure that transfection had occurred, cells were typically cotransfected with green fluorescent protein as a marker of transfection efficiency. Inhibition of Gβγ action had no effect on glucose- or GIP-stimulated AA release (βARKct expression versus pRK5 control; n = 3) or insulin secretion in βT3-3 cells (Fig. 5). In addition, pertussis toxin (100 and 500 ng/ml) had no effect on AA release, indicating that toxin sensitive Go-proteins (Goα, Goβ, and Goγ) do not play a role in glucose- or GIP-stimulated AA release in βT3-C3 cells (data not shown). This agrees with our previous studies showing that pertussis toxin at 500 ng/ml had no effect on cAMP levels in βT3-C3 cells (39). However, both the diterpene forskolin and the incretin GLP-1, agents that specifically elevate intracellular cAMP levels, were able to stimulate AA release (Fig. 6), indicating that GIP may be acting on AA release via stimula-

**FIG. 4. Effect of G protein βγ inhibition on GIP-mediated arachidonic acid release in rGIP-15 cells.** rGIP-15 cells expressing the GIP receptor were transiently transfected with 10 μg of pRK5 vector or βARKct cDNA construct, and the medium was removed at 45 min. AA efflux was measured as described under “Experimental Procedures.” The inset illustrates basal levels of AA release. *p < 0.05.

**FIG. 5. Effect of G protein βγ inhibition on glucose and GIP-potentiated insulin secretion in βT3-3 cells.** βT3-C3 cells expressing the GIP receptor were transiently transfected with 10 μg of pRK5 vector or βARKct cDNA construct as described under “Experimental Procedures.” Insulin secretion was assayed by radioimmunoassay and corrected for cell number by representation as the percentage of basal (n = 3). *, p < 0.05 for basal versus all; #, p < 0.05 for 11 mM glucose versus GIP; **, p < 0.05 for 10 mM GIP versus 100 mM GIP as tested by ANOVA.

The reduction of extracellular Ca2+ was found to have no effect on GIP-stimulated AA release, implying that a Ca2+-independent mechanism was involved in the production of AA (Fig. 8a). As predicted, neither glucose nor GIP was able to stimulate insulin secretion from βT3C3 cells under stringent Ca2+-free conditions (Fig. 8b). However, GIP was clearly still capable of elevating cAMP levels despite a reduction in basal cAMP production (Fig. 8c). The cAMP levels resulting from GIP stimulation under Ca2+-free conditions were, however, significantly suppressed compared with control conditions (p < 0.05).

The ability of GIP to release AA under Ca2+-free conditions suggested that a Ca2+-independent PLαγ was involved. An inhibitor specific for iPLA2, HEISS, has previously been shown to inhibit glucose-stimulated AA production and insulin secretion in several β-cell models (33, 44, 45). In the present study, HEISS was found to inhibit GIP-stimulated AA production as well as glucose- and GIP-stimulated insulin secretion (Fig. 9), supporting the aforementioned hypothesis that the enzyme coupled to GIP receptor signaling is a Ca2+-independent PLαγ.

**DISCUSSION**

In human type 2 diabetes there is a decreased insulin response to GIP that is of unknown etiology. One possible underlying defect is in the normal signal transduction pathways by which GIP stimulates insulin secretion in β-cells. It has been established that GIP stimulates adenylyl cyclase (13), increases intracellular Ca2+ (18), and activates mitogen-acti-
vated protein kinase (20), and the current study was undertaken to identify alternate mechanisms of regulating β-cell function. We have shown that GIP receptors in βTC-3 cells and transfected CHO-K1 cells are capable of coupling to transduction systems that release arachidonic acid from membrane lipids via activation of a Ca\(^{2+}\)-independent phospholipase A\(_2\). Additionally, this signaling pathway was shown to involve G protein βγ coupling in CHO-K1 cells, whereas a cyclic AMP-mediated pathway is probably involved in βTC-3 cells.

Initial studies of GIP-stimulated AA release revealed a marked difference in the time dependence of AA release between CHO-K1 and βTC-3 cells. The much more rapid release evident in rGIP-15 cells is in agreement with previously observed AA production rates observed with rhodopsin and muscarinic receptors expressed in CHO-K1 cells (41, 42) and other cell types (40, 46, 47). However, coupling of GIP to AA release was much slower in βTC-3 cells, suggesting a unique GIP receptor-AA coupling mechanism. There was also a difference between GIP- and glucose-induced AA release in βTC-3 cells, with GIP initiating release by 30 min, whereas glucose had no effect by this time (Fig. 3). This suggests that separate mechanisms couple glucose and the GIP receptor to AA production. Extensive studies have established that the glucose-induced AA production coupled to β-cell insulin secretion (24, 48) involved activation of an ATP sensitive, Ca\(^{2+}\)-independent PLA\(_2\) (27, 48). This enzyme has been identified in a number of insulinoma cell lines, including βTC-3 cells (44), and further studies were therefore performed to determine whether GIP-induced AA release also resulted from its activation.

The C-terminal fragment of the β-adrenergic receptor kinase

\[ \text{FIG. 6. A role for cAMP signaling as a mediator of arachidonic acid release in βTC-3 cells.} \]

\[ \text{FIG. 7. Effect of protein kinase A inhibition on GIP-mediated (a) and forskolin-mediated (b) arachidonic acid release in βTC-3 cells. The cells were preincubated for 15 min in 5 μM H89 prior to and during experiments. AA efflux was measured as described under "Experimental Procedures" (n ≥ 3). *}, p < 0.05. \]
protein (βARKct or G protein receptor kinase 2) was utilized to study the role of Gβγ signaling. Jelsema and Axelrod (35) first suggested that activation PLA2 can be performed by Gβγ subunits. In the present study it was found that the GIP receptor can couple to PLA2 via G protein βγ subunits in CHO-K1 cells, whereas neither glucose nor GIP-stimulated arachidonic release or insulin secretion were dependent on Gβγ subunit signaling in βTC-3 cells (Fig. 4). This is in contrast to their involvement in K⁺- and bombesin-stimulated insulin secretion in HIT-T15 cells (34). Further studies are needed to determine whether Gβγ subunits are involved in GIP receptor-effector coupling in other targets such as the stomach, fat, or the adrenal gland (49–51).

Glucose-, GIP-, and ATP-stimulated AA release were all shown to be independent of extracellular Ca²⁺, indicating that they are likely acting on a similar iPLA₂ isoform. Recently cholecystokinin, another insulinotropic peptide, was also shown to activate islet PLA₂ independently of extracellular Ca²⁺ (52). Despite a complete ablation of insulin release under Ca²⁺-free (extracellular) conditions, intracellular cAMP levels were still stimulated by GIP (Fig. 8 b), implying that this may be the proximal messenger to AA release. A reduction in basal cAMP production is likely attributable to a decrease in basal Ca²⁺-activated adenylyl cyclase activity, therefore accounting for the reduction in GIP-stimulated cAMP. From these observations it therefore seems likely that both GIP-stimulated cAMP and AA production are proximal signaling events independent of glucose and extracellular Ca²⁺ but insufficient to elicit insulin exocytosis. However, these signaling intermediates may play more direct roles in the actions of GIP under euglycemic conditions, such as those in the adipocyte (50).

In islets, glucose stimulation can elevate endogenously generated AA from the micromolar range to cellular concentrations of 50–200 μM, as measured by mass spectrometry (48). In agreement with work published by Metz (53), exogenous AA over this range was able to stimulate insulin release from βTC-3 cells in the presence of glucose. However, in its absence, responsiveness to AA was reduced at least 10-fold. Interestingly, application of exogenous AA has been shown to elevate intracellular Ca²⁺ concentrations in pancreatic islets (53), and there is considerable evidence suggesting a role for arachidonic acid itself or its metabolites in the regulation of capacitive and noncapacitive Ca²⁺ influx in a number of cellular systems (54, 55). Thus, it is tempting to speculate that fluxes in free endogenous AA, brought about by GIP, may play an integral role in regulating intracellular Ca²⁺ concentrations and thereby influence insulin secretion.

Our studies indicate that the mediation of GIP-stimulated PLA₂ activity probably occurs via cAMP actions in the β-cell. Because the specific iPLA₂ inhibitor HELSS ablated insulin responses to glucose and thus the potentiating effect of GIP...
(Fig. 9) the converging actions on insulin secretion of these two secretagogues may occur distal to the formation of cAMP (by GIP) and arachidonic acid (by glucose and/or GIP). Arachidonic acid and/or its metabolites may therefore be mainly involved in the fine tuning of the insulin response. The actions of cAMP could be direct, via activation of small G proteins (e.g., Rap), or through a guanine nucleotide exchange factor; however, the involvement of protein kinase A is unlikely (Fig. 7). These results are in contrast to a recent study demonstrating an inhibitory affect of cAMP and incretins (GIP and GLP-1) on CCK-8-stimulated arachidonic acid production and insulin release in the rodent islet (56). However, implicit in studies conducted with isolated islets is the existence of paracrine and endocrine interactions between α-, β-, and PP cells that contribute to a functional response. This may account for the different responses observed in the clonal cell line used in the present study.

Finally, in the current study, production of AA was assessed by measuring the total radioactivity secreted from βTC-3 cells. Although it has been shown in studies on tumor β-cell lines that a surprisingly small percentage of released radioactivity consists of metabolites (48), a recent study suggested a role for lipoxygenase-12 metabolites in β-cell function (57). Further studies need to be conducted to discriminate between AA and its metabolites produced by GIP stimulation of the β-cell.

Acknowledgments—We thank Dr. R. J. Lefkowitz for the pRK5 vector and βARKct construct, Simon Hinke for insight into the manuscript, and Cuilan Nian for technical support on this project.

REFERENCES
1. Pederson, R., Schubert, H. E., and Brown, J. C. (1975) Diabetes 24, 1050–1056
2. Falko, J. M., Crockett, S. E., Cataland S., and Mazzaferri E. L. (1975) J. Clin. Endocrinol. Metab. 41, 260–265
3. Cataland, S., Crockett, S. E., Brown J. C., and Mazzaferri, E. L. (1974) J. Clin. Endocrinol. Metab. 39, 223–228
4. Pederson, R., and Brown, J. C. (1976) Endocrinology 103, 610–615
5. Fehmann, H.-C., Goke, R., and Goke, B. (1995) Endocr. Rev. 16, 390–410
6. Nauck, M., Stuckman, R., Ebert, R., and Creutzfeldt, W. (1996) Diabetologia 39, 49–52
7. Holst, J., Gromada, J., and Nauck, M. (1997) Diabetologia 40, 984–986
8. Nauck, M., Heimesaat, M., Ørskov, C., Holst, J., Ebert, R., and Creutzfeldt, W. (1996) J. Clin. Invest. 97, 301–307
9. Udin, T., Meezy, E., Button, D., Brownstein, M., and Bonner, T. (1993) Endocrinology 133, 2861–2870
10. Wheeler, M., Geling, R., McIntosh, C., Georgiou, J., Brown, J., and Pederson, R. (1995) Endocrinology 136, 4629–4639
11. Gremlich, P., Forret, A., Hanli, E., Cherif, D., Vionnet, N., Bonne, P., and Thorens, B. (1999) Cell. Signal. 11, 405–415
12. Weiss, J. (1998) J. Biol. Chem. 273, 257–265
13. Efrat, S., Linde, S., Kofod, H., Spector, D., Delannoy, M., Grant, S., Hanahan, D., and Wolf, B. A. (1996) J. Biol. Chem. 271, 94–100
14. Saurvadet, A., Rohn, T., Pecker, F., and Pavoine, C. (1997) J. Biol. Chem. 272, 272, 7442–7452
15. Chen, M., Yang, Z., Naji, A., and Wolf, B. A. (1996) Endocrinology 137, 2901–2909
16. Loweth, A. C., Scarpello, J. H. B., Morgan, N. G. (1995) Mol. Cell. Endocrinol. 112, 177–183
17. Wahl, M., Plehn, R., Landsbeck, E., Verspohl, E., and Ammon, H. (1992) Mol. Cell. Endocrinol. 90, 117–123