Insulin Signals to Prenyltransferases via the Shc Branch of Intracellular Signaling*

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We assessed the roles of insulin receptor substrate-1 (IRS-1) and Shc in insulin action on farnesyltransferase (FTase) and geranylgeranyltransferase I (GGTase I) using Chinese hamster ovary (CHO) cells that overexpress wild-type human insulin receptors (CHO-hIR-WT) or mutant insulin receptors lacking the NPEY domain (CHO-ΔNPEY) or 3T3-L1 fibroblasts transfected with adenoviruses that express the PTB or SAIN domain of IRS-1 and Shc, the pleckstrin homology (PH) domain of IRS-1, or the Src homology 2 (SH2) domain of Shc. Insulin promoted phosphorylation of the α-subunit of FTase and GGTase I in CHO-hIR-WT cells, but was without effect in CHO-ΔNPEY cells. Insulin increased FTase and GGTase I activities and the amounts of prenylated Ras and RhoA proteins in CHO-hIR-WT (but not CHO-ΔNPEY) cells. Overexpression of the PTB or SAIN domain of IRS-1 (which blocked both IRS-1 and Shc signaling) prevented insulin-stimulated phosphorylation of the FTase and GGTase I α-subunit activation of FTase and GGTase I and subsequent increases in prenylated Ras and RhoA proteins. In contrast, overexpression of the IRS-1 PH domain, which impairs IRS-1 (but not Shc) signaling, did not alter insulin action on the prenyltransferases, but completely inhibited the insulin effect on the phosphorylation of IRS-1 and on the activation of phosphatidylinositol 3-kinase and Akt. Finally, overexpression of the Shc SH2 domain completely blocked the insulin effect on FTase and GGTase I activities without interfering with insulin signaling to MAPK. These data suggest that insulin signaling from its receptor to the prenyltransferases FTase and GGTase I is mediated by the Shc pathway, but not the IRS-1/phosphatidylinositol 3-kinase pathway. Shc-mediated insulin signaling to MAPK may be necessary (but not sufficient) for activation of prenyltransferase activity. An additional pathway involving the Shc SH2 domain may be necessary to mediate the insulin effect on FTase and GGTase I.

Although insulin is a weaker mitogen than many other growth factors, it is nevertheless essential for growth and differentiation of many, if not all, tissues and cell types. The mechanism of the mitogenic influence of insulin remains incompletely understood. It appears that activation of the Ras/MAPK1 and phosphatidylinositol (PI) 3-kinase pathways is necessary for the nuclear effects of insulin (1–6). Both DNA synthesis and transcription regulation have been shown to involve the MAPK and PI 3-kinase pathways (1–6).

We have recently identified another aspect of the mitogenic influence of insulin: its ability to stimulate the prenylation of the Ras family of GTPases (7, 8). Insulin promotes the phosphorylation and activation of farnesyltransferase (FTase) and geranylgeranyltransferases (GGTase) I and II (9–11). Activation of these enzymes results in increases in the amounts of prenylated Ras, Rho, and Rab proteins available for activation by other growth factors (9, 12). Cells grown in the presence of high concentrations of insulin and tissues of hyperinsulinemic animals contain increased amounts of farnesylated p21ras and geranylgeranylated RhoA (9–12). We have also shown that ambient hyperinsulinemia potentiates the mitogenic influence of insulin-like growth factor-1, epidermal growth factor, platelet-derived growth factor, and lysosphosphatic acid in a variety of tissues (9–13). These findings indicate that hyperinsulinemia creates a certain background for cellular responses to the mitogenic influence of other growth-promoting agents.

FTase and GGTase I are ubiquitous heterodimers, each consisting of an α- and a β-subunit (14). Although the β-subunit of each enzyme confers substrate specificity, these two prenyltransferases share a common α-subunit (15). We have previously shown that insulin promotes phosphorylation of the α-subunit and that this phosphorylation correlates with increased enzymatic activity of these enzymes (16). Insulin-induced phosphorylation of the α-subunit of FTase and GGTase I and subsequent activation of these enzymes require the presence of the intact C-terminal domain of the insulin receptor, is dependent on the activation of the Ras/MAPK pathway, and does not involve the PI 3-kinase pathway (16).

Because IRS and Shc proteins lie upstream of Ras in the relay of insulin signaling, we investigated the role of IRS-1 and Shc proteins in insulin signaling to the prenyltransferases. Since phosphorylation of IRS and Shc proteins requires the

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1 The abbreviations used are: MAPK, mitogen-activated protein kinase; PI, phosphatidylinositol; FTase, farnesyltransferase; GGTase, geranylgeranyltransferase; IRS, insulin receptor substrate; PH, pleckstrin homology; SH2, Src homology 2; CHO, Chinese hamster ovary; CMV, cytomegalovirus; Ad5, adenovirus type 5; MEK, mitogen-activated protein kinase/extracellular signal-regulated kinase kinase; PTB, phosphotyrosine binding; SAIN, shc and IRS-1 NPXY.
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presence of the NPEY domain of the insulin receptor (16, 17), we utilized a mutant insulin receptor with a deletion of the NPEY domain (ΔNPEY) to address this question. In addition, we employed adenoviral transduction of proteins (the PTB and SAIN domains of IRS-1 and Shc, the PH domain of IRS-1, and the Shc SH2 domain) that, when overexpressed, functionally eliminate the influence of endogenous IRS and/or Shc proteins. This approach allowed us to assess the roles of IRS and Shc proteins in the mechanism of insulin action on FTase and GGTase I in 3T3-L1 fibroblasts and Chinese hamster ovary (CHO) cells.

**EXPERIMENTAL PROCEDURES**

**Materials**—All standard chemicals were from Sigma. Anti-Ras monoclonal antibody was from Transduction Laboratories (Lexington, KY); anti-RhoA antibody was from Santa Cruz Biotechnology, Inc. (Santa Cruz, CA); anti-phosphoysrin antibody was from Sigma; and anti-ACTIVE MAPK was from Promega (Madison, WI). All supplies and reagents for SDS-polyacrylamide gel electrophoresis were from Bio-Rad, and the enhanced chemiluminescence kit was from Amersham Pharmacia Biotech. Recombinant Ras (Ras-CVLS) and Rho (Ras-CVLL) proteins were from Calbiochem. Insulin was from Lilly, and [32P]orthophosphate was from PerkinElmer Life Sciences. CHO cells (transfected with a plasmid for neomycin resistance) have been characterized and described previously (16).

**Phosphorylation Assay of IRS-1 and Shc Proteins in CHO-hIR-WT, ΔNPEY, and CHO-neo Cells**—Cells were preincubated in serum-free medium for 4 h and then incubated without or with 100 nM insulin for 5 min. Cell homogenates were prepared in lysis buffer (150 mM NaCl, 5 mM Tris, 10 mM Tris, 0.55 mM ATP, and 1 mM MgCl₂ (pH 7.5)) for 10 min at room temperature. Reactions were stopped by the addition of 8 x HCl followed by the addition of CHCl₃/methanol (1:1, v/v). Solutions were centrifuged at 14,000 rpm for 1 min. The organic layer was lyophilized and resuspended in methanol. Samples were loaded onto silica Gel 60 TLC plates that had been previously coated with 1% potassium oxalate. The samples were resolved in a solution of CHCl₃/methanol/H₂O (60:47:11:2). The TLC plates were dried and visualized by autoradiography.

**FTase and GGTase I Activity Assay**—Cells were challenged with 100 nM insulin for 1 or 24 h and then lysed in buffer. Prenyltransferase activity was assayed in vitro using a modified method of Moores et al. (20). Lysates containing endogenous FTase or GGTase I from control insulin-treated cells were normalized for protein. The in vitro assay was initiated by adding a 5 µl aliquot of normalized extract to 45 µl of a reaction assay solution (5 mM MgCl₂, 5 mM dithiothreitol, 100 mM Ras-CVLS (Ras) or Ras-CVLL (RhoA analog) protein, 100 mM tritiated farnesyl pyrophosphate (15 Ci/mmol) or geranylgeranylated pyrophosphate (15 Ci/mmol), respectively, and 50 mM HEPES, pH 7.5) and incubated at 37 °C for 30 min. The assay was terminated by the addition of 1 ml of 1 N HCl in ethanol, and the reaction mixture was filtered through Whatman GF/C glass-fiber filters and air-dried. Labelled protein (a measure of enzymatic activity) was quantified by liquid scintillation spectrometry.

**Assay for Amounts of Farnesylated p21ras** and Geranylgeranylated RhoA—Cells were incubated with or without insulin (100 nM) for 1 or 24 h and lysed. Normalized lysates were mixed with an equal volume of Triton X-114 and incubated at 37 °C for 3 min, and aqueous and detergent phases were allowed to separate at room temperature as previously described (7–12). Antibodies to p21ras or RhoA were used to immunoprecipitate their respective GTPases from both the aqueous (unprenylated GTPase) and detergent (prenylated GTPase) phases. Proteins were resolved by SDS-polyacrylamide gel electrophoresis, detected by Western blotting using anti-phosphotyrosine antibodies, and quantified by densitometry.

**RESULTS**

**Role of the NPEY Domain of the Insulin Receptor**—Initially, we assessed the effects of insulin on the phosphorylation and stimulation of FTase and GGTase I in CHO cells overexpressing the wild-type insulin receptor or a mutant lacking the NPEY domain (ΔNPEY). The NPEY domain is the site of IRS-1 and Shc binding to the cytoplasmic portion of the insulin receptor. The ΔNPEY cells contain 9 × 10⁴ mutant human insulin receptors/cell, similar to the cells transfected with the wild-type human insulin receptor (CHO-hIR-WT). The control CHO-neo cells (transfected with a plasmid for neomycin resistance) possess ~3000 rodent insulin receptors/cell. All three cell lines have been characterized and described previously (16).

Insulin (100 nM) promoted phosphorylation of IRS-1 and Shc in the CHO-hIR-WT cells (Figs. 1, A and B), but not in the ΔNPEY cells. There was a minimal but consistent effect of insulin in the CHO-neo cells, reflecting the presence of the NPEY domain (ΔNPEY). Since phosphorylation of Shc and IRS-1 is required for their association with Grb2, we assessed co-immunoprecipitation of Grb2 with either Shc or IRS-1 in cells expressing the wild-type and mutant insulin receptors. Insulin stimulated an association of Grb2 with Shc and IRS-1 in the CHO-hIR-WT cells, but not in the ΔNPEY cells (Fig. 1, C and D), confirming the lack of Shc- and IRS-1-mediated downstream signaling in these cells.
This page contains information about insulin signaling and prenyltransferases. It discusses the role of Shc versus IRS-1, insulin's effect on phosphorylation, and the interaction of the insulin receptor with IRS-1 or Shc. The text also mentions the prenyltransferases, FTase/GGTase I, and their activation by insulin. Additionally, it references studies involving adenoviral transduction of 3T3-L1 fibroblasts and the use of adenoviral vectors to study insulin signaling.
MAPK remained unaffected in these cells (Fig. 5). Thus, overexpression of the PH domain appears to be a useful tool in examining the influence of IRS-1 versus Shc pathways on prenyltransferases.

Overexpression of the PTB or SAIN domain of the IRS-1 and Shc proteins prevented the interaction of the endogenous domains of these intermediates with the juxtamembrane domain of the insulin receptor (18, 19) and thereby blocked insulin’s ability to promote phosphorylation of the \( \alpha \)-subunit of FTase/GGTase I (Fig. 6). In contrast, interference with the IRS-1 PH domain had no effect on this aspect of insulin action, suggesting that IRS-1 does not play a role in this process. Unexpectedly, we found that blocking the Shc SH2 domain completely inhibited the insulin effect on the phosphorylation of the \( \alpha \)-subunit of FTase/GGTase I (Fig. 6).

In concert with these observations, we found that functional disruption of IRS-1/SH2 binding to the insulin receptor by adenoviral transduction of the PTB and SAIN domain proteins also eliminated the ability of insulin to increase the activities of prenyltransferases and the amounts of farnesylated \( p21^{ras} \) and geranylgeranylated RhoA (Fig. 7, A–D). In contrast, overexpression of the IRS-1 PH domain did not impair the effect of insulin on either the FTase (Fig. 7A) or GGTase I (Fig. 7B) activity or on the amounts of farnesylated \( p21^{ras} \) (Fig. 7C) and geranylgeranylated RhoA (Fig. 7D), even though it completely blocked the IRS-1-related signaling. These observations argue against the role of IRS proteins in the mechanism of insulin action on prenyltransferases. Even though the Shc SH2 domain is not involved in Shc-insulin receptor interactions (25, 26), an interference with the Shc SH2 domain completely inhibited the insulin effect on the amounts of farnesylated \( p21^{ras} \) and geranylgeranylated RhoA (Fig. 7C and D).

Taken together, these findings indicated that interference with Shc binding (overexpression of the PTB or SAIN domain) to the insulin receptor blocked the insulin effect on prenyltransferases. In contrast, interference with IRS-1 binding alone (overexpression of the PH domain) did not block the insulin effect. Interestingly, interference with the Shc SH2 domain (a domain not needed for the interaction of Shc with the insulin receptor) (25) inhibited the effect of insulin on prenyltransferases, even though Shc continued to mediate an insulin effect on MAPK (Fig. 8).

Finally, we confirmed a lack of potential involvement of PI 3-kinase in this process using adenoviral transduction of the blocking peptide of either the p85 NSH2 domain or constitutively active p110. Neither of these transductions had any effect on the ability of insulin to stimulate FTase activity (Fig. 9A) or to increase the amounts of farnesylated \( p21^{ras} \) (Fig. 9B). Similar results were obtained in experiments with GGTase I (data not shown).
DISCUSSION

Insulin-specific stimulation of prenylation of the Ras family of small molecular mass GTPases has emerged as an important aspect of insulin action that modulates cellular mitogenic responses to a variety of growth factors (9, 11, 12). In previous studies, we identified several steps in the mechanism of insulin action on prenylation. We found that insulin promotes phosphorylation of the $\alpha$-subunit of FTase (which is shared with GGTase I) (9, 10) and the $\alpha$-subunit of GGTase II (27). This increase in phosphorylation of the corresponding $\alpha$-subunits appears to correlate with the activities of all three prenyltransferases (10, 27, 28). Augmented activities of FTase and GGTase I increase the amounts of prenylated p21\textsuperscript{ras} and RhoA, respectively, in cells exposed to high concentrations of insulin (7–13). Prenylation of p21\textsuperscript{ras} and RhoA GTPases is a prerequisite for their activation by GTP loading under the influence of other growth factors (14). Thus, by providing greater amounts of prenylated p21\textsuperscript{ras} and RhoA, hyperinsulinemia increases the mitogenic responsiveness of tissues to various growth-promoting agents. We have proposed that the “priming effect” of hyperinsulinemia plays a significant role in the cellular responsiveness to growth-promoting agents.

In this study, we first determined that disruption of the interaction of IRS-1 and Shc with the insulin receptor abrogates insulin effects on the prenyltransferases. Thus, an insulin effect was absent in cells overexpressing a mutant insulin receptor lacking the NPEY domain ($\Delta$NPEY) and in cells with

**Fig. 4.** Effect of overexpression of the PH domain peptide on insulin signaling via the IRS-1/PI 3-kinase branch. Cells were transduced with adenoviruses expressing the IRS-1 PH domain-blocking peptide or vector only (control) as described under “Experimental Procedures.” Cells were then treated with 100 nM insulin for either 10 min or 1 h as indicated and lysed. A, IRS-1 immunoprecipitates (IP) were immunoblotted (IB) with the PY20 antibody to determine phosphorylation of IRS-1. B, IRS-1 immunoprecipitates were blotted with the anti-P85 antibody to determine an association of IRS-1 with P85. C, IRS-1 immunoprecipitates were blotted with the anti-IRS-1 antibody to determine the amounts of IRS-1 protein in these samples. D, PI 3-kinase was activated by insulin (10 min) in the IRS-1 immunoprecipitates. Cells transduced with the Shc SH2 domain-blocking peptide were used as additional controls. E, shown are the results of the insulin-induced phosphorylation of Akt in cells transduced with the PH domain (a 10-min incubation with insulin).
FIG. 7. Effect of insulin on the activities of FTase and GGTase I and the amounts of prenylated p21\textsuperscript{ras} and RhoA in 3T3-L1 fibroblasts. Cells were transduced (as described in the legend to Fig. 6) and then incubated in medium without (open bars) or with (closed bars) insulin (100 nM) for 1 h. Endogenous FTase (A) and GGTase I (B) activities and the amounts of farnesylated p21\textsuperscript{ras} (C) and geranylgeranylated RhoA (D) were assayed in cell lysates as described under “Experimental Procedures.” Prenyltransferase activity is expressed as the mean ± S.E. of four experiments/group. *, p < 0.05 versus controls (CNT; no insulin) (A and B). The amounts of prenylated p21\textsuperscript{ras} and RhoA are expressed as percentages of total cellular p21\textsuperscript{ras} and RhoA, respectively, and are plotted as the means ± S.E. of four experiments/group. *, p < 0.05 versus controls (no insulin) (C and D).
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The overexpressed IRS-1 PH domain to block insulin signaling along the IRS-1 pathway without any effect on the Shc/MAPK pathway. In cells with overexpression of the IRS-1 PH domain, insulin failed to stimulate IRS-1 phosphorylation, association of p85 with IRS-1, and activation of PI 3-kinase and Akt (Fig. 4). In contrast, insulin still promoted phosphorylation of Shc and MAPK in these cells (Fig. 5). Thus, overexpression of the PH domain allows one to study the Shc/MAPK-mediated signaling independently of the IRS-1/PI 3-kinase signaling branch. The mechanism whereby interference with the PH domain blocks interactions of IRS-1 with the insulin receptor remains unknown. Because the PH domain of IRS-1 interacts with the plasma membrane, one can assume that the inability of IRS-1 to anchor at the plasma membrane precludes the interactions of its PTB domain with the insulin receptor. Further studies are needed to detail this process. For the purpose of our investigation, we demonstrated that the blockade of insulin signaling via the IRS-1 pathway with overexpression of the IRS-1 PH domain does not interfere with the ability of insulin to activate the prenyltransferases and to augment prenylation of Ras and Rho proteins.

Another novel and unexpected observation was made when we blocked the Shc SH2 domain. A functional knockout of this domain prevented insulin action on the prenyltransferases. In cells transduced with the anti-Shc SH2 protein antibody, insulin failed to stimulate phosphorylation of the γ-subunit (Fig. 6), activation of the prenyltransferases (Figs. 7, A and B), and augmentation of the amounts of prenylated GTPases (Figs. 7, C and D). In contrast, insulin continued to activate MAPK in these cells (Fig. 8). The Shc SH2 domain is not involved in binding of Shc to the insulin receptor (25, 26); and in fact, its function in the mechanism of insulin signaling remains obscure. We propose that a new role for this domain is to mediate insulin signaling to the prenyltransferases. The precise biochemical role of this domain in mediating insulin signaling to prenyltransferases remains enigmatic. A possible unknown and yet to be characterized docking intermediate(s) may be necessary for the propagation of insulin signaling mediated through the Shc SH2 domain.

We have previously demonstrated that the insulin-induced signaling to the prenyltransferases involves activation of the Ras/MAPK pathway (10). Cells with a dominant-negative mutant of Ras and cells treated with PD98059, an inhibitor of MEK, fail to respond to insulin in terms of stimulation of the prenyltransferases (10). These observations suggest that insulin stimulates the prenyltransferases in a positive feedback fashion. Insulin activates p21ras and promotes the phosphorylation and activation of MAPK. The latter appears to phosphorylate and activate FTase, which, in turn, farnesylates more p21ras, allowing farnesylated p21ras to anchor at the plasma membrane in preparation for subsequent activation (12). What remains unresolved is an important question as to why other growth factors that activate MAPK fail to mimic the insulin effect on the prenyltransferases.

One possibility is that activation of MAPK is a necessary (but not sufficient) step for activation of the prenyltransferases by insulin. Conceivably, the putative additional steps that complement the influence of MAPK are exclusively under insulin’s control. In addition to the MAPK pathway, signaling via the PI 3-kinase pathway is equally important for mitogenesis (1–3). These two pathways may interact in mediating the insulin effect on the prenyltransferases. However, using Wortmannin, an inhibitor of PI 3-kinase, we have previously demonstrated that inhibition of PI 3-kinase has no effect on the ability of insulin to activate the prenyltransferases (10). The present study is in agreement and demonstrates that neither a functional

Fig. 8. Effect of insulin on the phosphorylation of MAPK in wild-type and transduced (Shc SH2 domain-blocking peptide) 3T3-L1 fibroblasts. Wild-type (WT) fibroblasts or fibroblasts transduced with adenoviruses expressing the p85 NSH2 peptide were incubated without or with insulin (100 nM) for 5 min. Cell lysates were normalized for protein and resolved on 12% polyacrylamide gels. The amounts of phosphorylation were determined by Western blotting using anti-phospho-MAPK antibodies. CNT, control.

Fig. 9. Effect of insulin on FTase activity and the amounts of farnesylated p21ras in 3T3-L1 fibroblasts. Wild-type (WT) and 3T3-L1 cells transduced with adenoviruses expressing the p85 SH2 and constitutively active p110 (p110 CAAX) peptides of PI 3-kinase were incubated in medium without (open bars) or with (closed bars) 100 nM insulin for 1 h. A, FTase activity is expressed as the mean ± S.E. of three experiments/group. *, p < 0.05 versus controls (no insulin). B, the amounts of farnesylated p21ras are expressed as a percentage of total cellular p21ras, and results represent the mean ± S.E. of three experiments. *, p < 0.05 versus controls (no insulin).
knockout of PI 3-kinase (overexpression of either the IRS-1 PH domain or the p85 NSH2 domain) nor constitutively active p110α has any effect on the insulin-stimulated prenylation.

The present findings also indicate that activation of MAPK is not sufficient to phosphorylate and activate the prenyltransferases. Thus, overexpression of the Shc SH2 domain resulted in full activation of MAPK in response to insulin, but a complete block in activation of the prenyltransferases. In summary, these experiments emphasize the importance of the Shc-mediated signaling from the insulin receptor to FTase and GGTase I. Downstream from Shc, this signal appears to proceed along two pathways. It involves activation of the MAPK pathway (29–31) and a yet unidentified pathway that involves the Shc SH2 domain. Both branches are necessary, but neither one alone is sufficient to promote the phosphorylation and activation of the prenyltransferases by insulin. The Shc SH2 domain may recruit additional proteins (possibly kinases) into this process. Further studies are needed to identify these putative intermediates.

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