A Synthetic Peptide Corresponding to the Rab4 Hypervariable Carboxyl-terminal Domain Inhibits Insulin Action on Glucose Transport in Rat Adipocytes*

(Received for publication, August 28, 1995, and in revised form, January 30, 1996)

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The present study was conducted to examine the involvement of Rab4, a low molecular weight GTP-binding protein, in the action of insulin on glucose transport. A synthetic peptide corresponding to the Rab4 hypervariable carboxyl-terminal domain, Rab4-(191–210), was successfully transferred into rat adipocytes by electroporation and inhibited insulin-stimulated glucose transport by about 50% without affecting the basal transport activity. In contrast, synthetic peptides corresponding to the Rab3C and Rab3D carboxyl-terminal hypervariable domain had little effect on insulin action on glucose transport. The Rab4-(191–210) peptide also reduced insulin-induced GLUT4 translocation from the intracellular pool to the plasma membrane. Furthermore, the Rab4-(191–210) peptide reduced both insulin-induced glucose transport and GLUT4 translocation in the presence of a major histocompatibility complex class I antigen-derived peptide, D(62–85), which is a potent inhibitor of GLUT4 internalization, suggesting that the peptide inhibited exocytotic recruitment of GLUT4-containing vesicles. The Rab4-(191–210) peptide also inhibited GTPγS-stimulated glucose transport. In addition, insulin-stimulated glucose transport was inhibited by the addition of anti-Rab4 antibody. These results suggest that Rab4 protein plays a crucial role in insulin action on GLUT4 translocation, especially in exocytotic recruitment by the hormone of the glucose transporter to the plasma membrane from the intracellular retention pool.

Insulin stimulates glucose uptake in skeletal/cardiac muscles and adipocytes by promotion of translocation of glucose transporter isoform, GLUT4, from the intracellular pool to the plasma membrane (1–3). Although the precise mechanism(s) of insulin-induced GLUT4 redistribution is still unclear, several lines of evidence indicate that GTP-binding protein(s) is involved in the insulin action. Thus, nonhydrolyzable GTP analogues induce GLUT4 translocation (4, 5) and stimulate glucose transport (6, 7) in permeabilized adipocytes. Furthermore, by dissecting the recycling pathway of GLUT4 into exocytosis and endocytosis, we have demonstrated recently that GTPγS stimulates exocytotic fusion of GLUT4-containing vesicles, whereas the nucleotide inhibits endocytosis of the glucose transporter (8). Our previous study also indicated that the number of GLUT4 molecules in recycling pool is not large in the basal state and the rate-limiting step of insulin-induced redistribution of GLUT4 is the exocytotic recruitment from the intracellular retention pool to the plasma membrane (8).

The Rab family proteins of Ras-related small GTP-binding proteins have been implicated in regulation of intracellular vesicular traffic (9). Given that exocytotic movement of vesicles is regulated by the Rab family protein(s), GTPγS may promote exocytosis of GLUT4-containing vesicles by stimulation of the Rab protein(s) associated with the vesicles, although other candidates (e.g. trimeric GTP-binding proteins) cannot be ruled out. In this regard, Baldini et al. (10) reported that Rab3D is predominantly expressed in adipocytes and is induced during differentiation of 3T3-L1 cells into adipocytes. However, it remains to be demonstrated whether Rab3D is associated with the GLUT4-containing vesicles (11). On the other hand, Cormont et al. (12) recently revealed that Rab4 is associated with GLUT4-containing vesicles in rat adipocytes and insulin stimulation resulted in redistribution of the protein from the vesicle to the cytosol. In contrast, Uphues et al. (13) reported that Rab4A was barely detectable in GLUT4-containing vesicles in rat cardiac muscle, although insulin induced an extensive shift of Rab4A from the cytosol and the microsomal fraction to the plasma membrane.

In order to investigate whether Rab4 plays an essential role in insulin-induced GLUT4 translocation, we incorporated a synthetic peptide corresponding to the Rab4 hypervariable carboxyl-terminal domain into rat adipocytes and examined its effect on the insulin action. The carboxy-terminal domain of Rab family proteins is thought to be responsible for targetting the proteins to the appropriate subcellular membranes (14) and to interact with the guanosine diphosphate dissociation inhibitor (15). Perez et al. (16) reported that synthetic peptides corresponding to the carboxy-terminal domains of Rab3B and Rab3C blocked calcium-triggered prolactin release from anterior pituitary cells. Our study shows that the insulin-induced GLUT4 translocation was markedly inhibited by incorporation of the Rab4 carboxyl-terminal domain peptide, suggesting that Rab4 protein plays a crucial role in the insulin-stimulated glucose transport in rat adipocytes.

EXPERIMENTAL PROCEDURES

Materials—GTPγS was purchased from Boehringer Mannheim. 125I-Labeled protein A was from DuPont NEN.

Rab Peptides and Anti-Rab4 Antibodies—The Rab4-(191–210) peptide (DAALRQLRSPRTOAPSQOE), Rab3C-(196–215) peptide (ITAKONTKLKTPPPPHPN), and Rab3o-(197–216) peptide (PGSNGKGPALGDTPPPQPS), derived from the carboxy-terminal domains of rat Rab4 (17), bovine Rab3C (18), and mouse Rab3D (10), respectively, were synthesized and purified by high pressure liquid chromatography to 85–95% homogeneity. Polyclonal antibodies against rat Rab4 were raised in this laboratory by immunizing a guinea pig with peptide
(C)QLRSPRTQAPSQAQ conjugated with keyhole limpet hemocyanine. When immunoblot was performed using total homogenate of rat adipocytes, a single band with a molecular size of 25 kDa was recognized with the anti-Rab4 antibodies.

Major Histocompatibility Complex Class I-derived Peptide—The D9-(62-85) peptide (RETIQAKGNEQSFRLDDLTRLKRYY), derived from the a1 domain of the murine major histocompatibility complex class I antigen (H-2D9), was synthesized in this laboratory as described previously (8). Peptide was dissolved to a concentration of 1.0 mM in 0.1 M NaCl and activated by incubation at 37 °C overnight prior to the addition to cells.

Preparation of Rat Adipocyte Cells—Isolated adipocytes were prepared by the collagenase method from epididymal adipose tissues of Sprague-Dawley rats (from Charles River, approximately 170–200 g) (19). Unless otherwise specified, isolated cells were suspended in Buffer A (25 mM K-ribosyl-Heneselel Hepes buffer supplemented with 20 mg/ml bovine serum albumin (Fraction V) and 3 mM pyruvate, pH 7.4).

Transfer of Rab4 Peptides or Anti-Rab4 IgG into Rat Adipocytes by Electroporation—The isolated cells were washed and resuspended in high K+/low Ca2+ buffer designated as Buffer X (118.0 mM KCl, 4.74 mM NaCl, 0.38 mM CaCl2, 10 mM EGTA, 1.18 mM MgSO4, 1.18 mM KH2PO4, 3.4 mM Hesper/KOH, 20 mg/ml bovine serum albumin, 3 mM pyruvate, pH 7.4) (20) and incubated for 30 min at 37 °C. Then, a 0.6-ml aliquot of the cell suspension was mixed with 0.15 ml of Rab4-(191–210) peptide or anti-Rab4 IgG solution, and the electroporation was carried out two times in a Gene-Pulser (Bio-Rad) set at 25 microfarads and 2.5 kV/cm.

Measurement of 3-O-Methyl-d-glucose Uptake—The cellular glucose transport activity was estimated by measuring the rate of 0.1 mM 3-O-methyl-d-glucose uptake by the oil flotation method as described previously (20).

Preparation of Subcellular Membrane Fractions—The plasma membrane and slowly sedimenting fractions, both enriched with glucose transporter, were prepared by differential and sucrose density gradient centrifugation as described by Kono et al. (21). The slowly sedimenting fraction (22) was identical to what had previously been referred to as the Golgi-rich fraction or the low density microsomal fraction (22) was identical to what had previously been referred to as the Golgi-rich fraction or the low density microsomal fraction. Centrifugation was blocked with solution containing 5% bovine serum albumin, 10 mM Tris/HCl (pH 7.5), 154 mM NaCl, 0.38 mM CaCl2, 1.0 mM EGTA, 1.18 mM MgSO4, 1.18 mM KH2PO4, 23.4 mM Hesper/KOH, 20 mg/ml bovine serum albumin, 3 mM pyruvate, pH 7.4) (20) and incubated for 30 min at 37 °C. Then, a 0.6-ml aliquot of the cell suspension was mixed with 0.15 ml of Rab4-(191–210) peptide or anti-Rab4 IgG solution, and the electroporation was carried out two times in a Gene-Pulser (Bio-Rad) set at 25 microfarads and 2.5 kV/cm.

RESULTS

In the present study, we first examined whether a sufficient amount of the Rab4-(191–210) peptide could be transferred into rat adipocytes by electroporation and whether transferred peptides had any effect on insulin action on glucose transport. As shown in Fig. 1, neither the basal nor the insulin-stimulated glucose transport activity was affected by the Rab4-(191–210) peptides in intact cells, whereas the insulin effect was reduced by about 50% in cells electroporated in the presence of the peptide. The extent of inhibition of insulin-stimulated glucose transport by the peptide varied from 30 to 90% (data not shown) probably because the efficiency of transfer of the peptide by electroporation was not consistent among the batches of cells. These results indicate that the Rab4-(191–210) peptides were successfully transferred into the cells by electroporation and inhibited insulin action on glucose transport.

As presented in Fig. 2, the Rab4-(191–210) peptide inhibited the insulin-stimulated glucose transport in a dose-dependent manner without affecting the basal transport activity. In contrast, a synthetic peptide of the Rab3C carboxy-terminal domain, which was shown to inhibit prolactin release in anterior pituitary cells (16), had little effect on the insulin-induced glucose transport. Similarly, a synthetic peptide of the Rab3D carboxy-terminal domain did not affect the insulin-induced glucose transport (data not shown). These results suggest that the insulin action was specifically inhibited by the Rab4-(191–210) peptide.
attenuating GLUT4 translocation from the intracellular pool to the plasma membrane. These results also provide evidence that Rab4 protein plays an essential role in insulin-induced GLUT4 translocation.

In the next set of experiments, we studied the effect of the Rab4-(191–210) peptide on insulin-stimulated glucose transport in the presence of the major histocompatibility complex class I antigen-derived peptide, Dk-(62–85), which is a potent inhibitor of endocytosis of GLUT4 (24). As reported previously (8), under these conditions, exclusively exocytotic accumulation of GLUT4 on the plasma membrane could be measured. As illustrated in Fig. 4, Rab4-(191–210) peptide inhibited insulin-induced glucose transport by about 40% in the presence of Dk-(62–85) without affecting the basal transport activity. Likewise, GLUT4 translocation by insulin in the presence of Dk-(62–85) was significantly inhibited by the Rab4-(191–210) peptide (Fig. 5). These results indicate that the Rab4-(191–210) peptide inhibited exocytotic recruitment by insulin of GLUT4 to the plasma membrane from the intracellular pool.

Studies from many laboratories including ours (4–7) showed that nonhydrolyzable GTP analogues stimulate GLUT4 translocation. Furthermore, by dissecting the recycling pathway of GLUT4 into exocytosis and endocytosis, we have demonstrated that GTPγS promotes exocytotic fusion of the GLUT4-containing vesicles (8). These observations led us to investigate whether the Rab4-(191–210) peptide inhibits the GTPγS-stimulated glucose transport. As presented in Fig. 6, the glucose transport activity stimulated by 1 mM GTPγS was reduced by about 40% in the cells electroporated with the Rab4-(191–210) peptide but not with the Rab3C-(196–215) peptides.

In the final set of experiments, we examined the effect of anti-Rab4 antibodies on insulin-induced glucose transport activity. A number of studies have demonstrated that electroporation can be employed to introduce antibodies into mammalian cells without affecting the physiological integrity of the cells (25–28). As shown in Fig. 7, in adipocytes electroporated in the presence of anti-Rab4 IgG, insulin effect on glucose transport was markedly attenuated. In contrast, nonimmune IgG did not show any inhibitory effect on insulin-induced glucose transport. The anti-Rab4 IgG was ineffective on the insulin action in intact cells (data not shown). These results provide further evidence for the aforementioned notion that Rab4 protein plays an essential role in the insulin action on glucose transport.

**DISCUSSION**

The Rab4 is a member of the Rab family of Ras-related small GTP-binding proteins and has been found to be associated with early endosomes in Chinese hamster ovary cells (29) or HepG2 cells (30). Functionally, Rab4 has been shown to control recycling of transferrin receptor from the early endosome to the cell surface (31). Cormont et al. (12) have recently revealed that Rab4 is present in the GLUT4-containing vesicles in rat adipocytes, and insulin stimulation resulted in redistribution of the protein from the vesicles to the cytosol. They also reported that Rab4 is phosphorylated by the insulin-stimulated MAP kinase (32) and argued that the insulin-induced redistribution of Rab4 from the GLUT4-containing vesicles to the cytosol could result from Rab4 phosphorylation by the kinase. Although the significance of Rab4 phosphorylation and redistribution in the insulin-stimulated GLUT4 translocation is yet to be clarified, the presence of Rab4 in the GLUT4-containing vesicles implies the endosomal origin of the vesicles and raises
the possibility that Rab4 may play an essential role in the insulin action.

In the present study, to investigate the physiological significance of Rab4 protein in the insulin action on glucose transport, we incorporated a synthetic peptide corresponding to the hypervariable carboxyl-terminal domain of Rab4 into rat adipocytes. The carboxyl-terminal domain of Rab family proteins is highly divergent (33) and contains structural elements necessary for the association of the proteins with specific target membranes (14). Synthetic peptides corresponding to the carboxyl-terminal domain of Rab3B and Rab3C have been shown to block calcium-triggered prolactin release from pituitary cells (16). As illustrated in Fig. 1, the Rab4-(191–210) peptide was successfully transferred into rat adipocytes by electroporation and inhibited insulin action on glucose transport. Immunoblot analysis indicated that the peptide significantly attenuated the insulin-induced GLUT4 translocation from the intracellular pool to the plasma membrane (Fig. 3). The inhibitory effects were specific to Rab4 because synthetic peptides of the Rab3C and Rab3D carboxyl-terminal domain were without effect.

Importantly, the inhibition by the peptide was also observed in the presence of a major histocompatibility complex class I antigen-derived peptide, Dk-(62–85), a potent inhibitor of insulin-stimulated glucose transport in the presence of Dk-(62–85) peptide. Adipocytes in Buffer X were incubated for 60 min at 37°C to stabilize the basal transport activity and then electroporated in the absence or the presence of 0.4 mM Rab4-(191–210) peptide. The cells were then incubated for 30 min in the absence (right panel) or the presence (left panel) of 50 μM Dk-(62–85) without (○) or with (●) 100 nM insulin, and the glucose transport activity was assayed. The results are the means ± S.E. (n = 3).

At present, the mechanism of the inhibition by the Rab4-(191–210) peptide is not clear. Because the carboxyl-terminal domain of Rab proteins contains structural elements necessary for the association with specific target membranes (14), the

![Fig. 4. Inhibition by Rab4-(191–210) peptide of the insulin-stimulated glucose transport in the presence of Dk-(62–85) peptide. Adipocytes in Buffer X were incubated for 60 min at 37°C to stabilize the basal transport activity and then electroporated in the absence or the presence of 0.4 mM Rab4-(191–210) peptide. The cells were then incubated for 30 min in the absence (right panel) or the presence (left panel) of 50 μM Dk-(62–85) without (○) or with (●) 100 nM insulin, and the glucose transport activity was assayed. The results are the means ± S.E. (n = 3).](image)

![Fig. 5. Inhibition by Rab4-(191–210) peptide of the insulin-stimulated GLUT4 translocation in the presence of Dk-(62–85) peptide. Adipocytes in Buffer X were incubated for 60 min at 37°C to stabilize the basal transport activity and then electroporated in the absence or the presence of 0.4 mM Rab4-(191–210) peptide. The cells were then incubated for 30 min in the presence of 50 μM Dk-(62–85) with or without 100 nM insulin. At the end of the incubation, the cells were washed, homogenized, and subjected to subcellular fractionation and immunoblotting as described under “Experimental Procedures.” A, representative immunoblot data. PM, plasma membrane fractions; SS, slowly sedimenting fractions. B, relative amounts of GLUT4. The relative intensities of GLUT4 bands were quantified by using FUJIX BAS2000 bio-imaging analyzer. The results are the means ± S.D. of three determinations. *, p < 0.05.](image)
Rab4-(191–210) peptide probably competes with endogenous Rab4 at the target sites. In agreement with the study by Perez et al. (16), the absence in Rab4-(191–210) peptide of two cysteine residues necessary for geranylgeranylation (34) seems to exclude Rab-guanosine diphosphate dissociation inhibitor as one of the target molecule because Rab-guanosine diphosphate dissociation inhibitor only associates with geranylgeranylated Rab protein (35). Further studies are dearly needed to identify the target molecules of the Rab4-(191–210) peptide.

Rab4 has been shown to control recycling of transferrin receptor from the early endosome to the cell surface (31). In Chinese hamster ovary cells expressing a mutant Rab4, transferrin receptor remains intracellular (31). These observations raise a possibility that the inhibition by the Rab4-(191–210) peptide of the insulin action may result from the reduction of the insulin receptor number on the cell surface. However, reduction of the receptor number may not account for the inhibition of glucose transport by the peptide, because the Rab4-(191–210) peptide also inhibited the glucose transport stimulated by GTP\(_S\) (Fig. 6). The effect of GTP\(_S\) on exocytosis of GLUT4-containing vesicles was not blocked by wortmannin, a potent and specific inhibitor of phosphatidylinositol 3-kinase (36), an observation indicating that GTP\(_S\) acts at a step(s) distal to phosphatidylinositol 3-kinase presumably by a direct interaction with vesicle trafficking machinery. Furthermore, as shown in Figs. 4 and 5, the inhibitory effect of the Rab4-(191–210) peptide on the insulin action was also observed in the presence of D\(_{22}(62–85)\). Because the D\(_{22}(62–85)\)peptide is a potent inhibitor of the internalization of the insulin receptor (37) as well as GLUT4, the insulin receptor remains on the cell surface in the presence of the peptide. The notion that Rab4 is involved in the insulin action on glucose transport is further supported by the experiment using antibodies against the carboxyl-terminal domain of Rab4. As demonstrated in Fig. 7, the anti-Rab4 antibody markedly reduced the insulin-stimulated glucose transport without affecting the basal transport activity. Hence, in the present study, two independent methods to modify the function of the Rab4 carboxyl-terminal domain provided essentially similar results. In summary, the present results demonstrate that a synthetic peptide corresponding to the Rab4 hypervariable domain specifically inhibits the insulin-stimulated glucose transport as well as GLUT4 translocation, providing evidence that Rab4 is involved in the insulin action, especially in exocytotic recruitment by the hormone of the glucose transporter to the plasma membrane from the intracellular pool. In the light of the observation that insulin stimulates exocytosis of the receptors for transferrin (42), it would be very intriguing to examine whether the Rab4 function is directly activated by the hormone or not.

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J. Biol. Chem. 1996, 271:9704-9709.
doi: 10.1074/jbc.271.16.9704

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