Evidence That Translocation of the Glucose Transport Activity Is the Major Mechanism of Insulin Action on Glucose Transport in Fat Cells*

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The glucose transport activity associated with the plasma membrane-rich and Golgi-rich fractions of fat cells was determined after they were reconstituted into egg lecithin liposomes. When the two subcellular fractions were isolated under conditions that would minimize their cross-contamination, the transport activity in the plasma membrane-rich fraction was found to be increased 6.3- to 8.6-fold by insulin, which was added to cells before homogenization, and that the activity in the Golgi-rich fraction was reduced approximately to one-half. In this study, the glucose transport activity in the plasma membrane-rich fraction (either in the basal or plus insulin state) was solubilized, reconstituted, and assayed with an overall efficiency of 23-35%.

Four agents known to have insulin-like effects on the glucose transport activity in intact fat cells (hydrogen peroxide, sodium vanadate, trypsin, and p-chloromercuriphenyl sulfonate) not only increased the transport activity in the plasma membrane-rich fraction, but also decreased the activity in the Golgi-rich fraction. The effect of hydrogen peroxide, unlike that of insulin, was not abolished when the insulin receptor was modified proteolytically.

Upon administration of insulin to fat cells, and subsequent elimination of the hormone, the glucose transport activities associated with the plasma membrane-rich and Golgi-rich fractions were affected almost concomitantly towards opposite directions. It is proposed as a working hypothesis that translocation of the glucose transport system to the plasma membrane from the Golgi-rich fraction is the major, if not the sole, mechanism by which insulin stimulates glucose transport in fat cells.

It was recently proposed from this and other laboratories that insulin stimulates glucose transport in fat cells by inducing translocation of the glucose transport mechanism from an intracellular storage site to the plasma membrane (1-4). One of the bases of this proposal is our finding that insulin increases the glucose transport activity in the plasma membrane fraction while decreasing the activity in the Golgi-rich fraction. In this study, we measured the glucose transport activity associated with the subcellular fraction by reconstituting it into egg lecithin liposomes (1, 2). Independently, Cushman and Wardzala (3) discovered that insulin increases the pH-glucose-inhibitable cytochalasin B-binding activity in the plasma membrane fraction while decreasing the activity in the microsomal fraction. Since cytochalasin B is a competitive inhibitor of glucose transport, it was postulated that the above binding would show the number of the glucose transport carriers.

The effect of insulin observed in both of the above studies were highly significant; thus, the hormone-dependent increase in the transport activity detected in our reconstituted plasma membrane-rich fraction was 2.0- to 2.5-fold (1, 2), and the corresponding value reported by Cushman and Wardzala was 3.1-fold (3). Nevertheless, these values are considerably less than that routinely observed in the glucose transport activity in intact fat cells, which is 5- to 10-fold (e.g. see Ref. 5). Therefore, it was yet to be ascertained whether the proposed translocation is the major mechanism, or merely represents a small fraction of the multiple mechanisms, by which insulin stimulates glucose transport in fat cells.

In our present study, we examined the possibility that the apparent effect of insulin estimated in the isolated plasma membrane-rich fraction might be increased if its contamination by the Golgi-rich fraction is minimized. As we pointed out previously (2), the low insulin effect observed in our previous work might be an artifact of cross-contamination between the two subcellular fractions which contained glucose transport activities that were affected by insulin towards the opposite directions. In addition, we examined in our present study whether the apparent translocation is induced not only by insulin but also by other agents that are known to have insulin-like activities. Finally, we re-examined the time courses of the development and reversal of insulin effects on the glucose transport activity associated with subcellular structures.

MATERIALS AND METHODS
Labeled 3-0-[3H]methyl-D-glucose and 2-deoxy-2-[3H(G)]glucose were purchased from New England Nuclear. These agents, both in ethanol solution, were dried in a stream of air and then dissolved into appropriate buffers. Sodium vanadate and hydrogen peroxide were purchased from Fisher; the concentration of the latter agent was determined by titration with potassium permanganate. Trypsin and soybean trypsin inhibitor were obtained from Worthington, and p-chloromercuriphenyl sulfonate was bought from Sigma. The sources of other materials were listed in our previous publications (1, 2). Isolated fat cells were prepared by the collagenase method (6) from epididymal adipose tissue of Sprague-Dawley rats weighing approximately 180-220 g (Madison Farm of Harlan Co.). Routinely, cells isolated from several rats were pooled and then divided into aliquots. Typically, each aliquot consisted of fat cells isolated from 1.5 rats suspended in 10 ml (total volume including cell) of Krebs-Henseleit 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid buffer (7) supplemented with 2 mM glucose, 20 mg/ml of bovine serum albumin (Fraction V), and the indicated agents. Insulin treatment was carried out with a 1 nM concentration of the hormone for 10 min after 30 min of preliminary incubation (2).

The incubated cells were washed and homogenized in a buffer containing 0.25 M sucrose, 1 mM EDTA (sodium salt, adjusted to pH 7.5), and 10 mM Tris-HCl, pH 7.5 (Buffer A) as previously described.
Insulin Action on Glucose Transport

The homogenate was fractionated by two methods designated as Method A and B. In Method A, the homogenate was centrifuged for 2 min (including approximately 25 s of acceleration time but excluding approximately 60 s of deceleration time) in a Beckman J-21 centrifuge set at 5,000 rpm (3,000 × gmax). All the centrifugations, including this one, were carried out at 2 °C. The pellet (P-1) and the fat fraction were discarded, and the infranatant solution (S-1) was centrifuged in a Beckman TI 75 rotor for 60 min at 60,000 rpm (340,000 × gmax; ω² = 1.28 × 10⁵). The supernatant solution (S-2) was discarded, and the pellet (P-2) was suspended in 0.7 ml of ice-cold Buffer B. The suspension was layered on top of a linear sucrose density gradient (approximately 1.4 × 8.5 cm in size) and centrifuged in a Beckman SW 41 rotor for 40 min at 25,000 rpm (200,000 × gmax). The sucrose concentration at the bottom of the gradient was 32.5% (w/w) and that at the top was 15.0% (w/w); the sucrose solution was supplemented with 1 mM EDTA (Na) and buffered with 10 mM Tris-HCl, pH 7.5. After the centrifugation, the sucrose solution (including 0.7 ml of Buffer A at the top) was drained from the bottom of the centrifuge tube and separated into 17 fractions (0.75 ml each). The plasma membrane-rich fraction (Fractions 3 through 7) and the Golgi-rich fraction (Fractions 13 through 17) were separately pooled, diluted with 2 ml of 1 mM EDTA (Na) in 10 mM Tris-HCl, pH 7.5, and centrifuged in a Beckman TI 75 rotor for 60 min at 60,000 rpm. The pellet obtained by this centrifugation (P-2b) and that obtained earlier (P-2a) were separately suspended in Buffer A and subjected to sucrose density gradient centrifugation as described in Method A. The plasma membrane-rich fraction (Fractions 3 through 7 of Fraction P-2a) and the Golgi-rich fraction (Fractions 13 through 17 of Fraction P-2b) were separately pooled, diluted, and centrifuged as in Method A.

In either Method A or Method B, the final pellet was dissolved in 220 pl of 20 mM sodium cholate in 10 mM Tris-HCl, pH 7.5, and frozen, as previously described (2, 8). The frozen preparation was thawed in water at room temperature, and a 200-μl portion was applied to a column of Sephadex G-50 (0.7 x 2.6 cm = 1 ml) equilibrated with 10 mM Tris-HCl, pH 7.5, and frozen, 2. The data in these figures further show that the 5'-nucleotide

RESULTS

Apparent Insulin Effects Observed in Isolated Subcellular Fractions—Figs. 1 and 2 show typical results of fractionation carried out by Method A (Fig. 1) and Method B (Fig. 2) as described under "Materials and Methods." These figures indicate that the glucose transport activities associated with the plasma membrane-rich fraction (Fractions 3-7) and the Golgi-rich fraction (Fractions 13-17) were well separated from each other, especially by Method B. The insulin-dependent increase in the glucose transport activity in the plasma membrane peak was approximately 7-fold in Fig. 1 and almost 10-fold in Fig. 2. The glucose transport activity in the Golgi peak was reduced almost to one-half by insulin in both Figs. 1 and 2. The data in these figures further show that the 5'-nucleotide

FIG. 1. Results of fractionation of fat cell homogenates by Method A. The basal and insulin-treated fat cells were homogenized and fractionated through the step of sucrose density gradient centrifugation by Method A (see "Materials and Methods"). The sucrose concentration in Fraction 1 was 32.5% (w/w), and that in Fraction 16 was 15.0% (w/w); Fraction 17 mostly consisted of Buffer A in which the sucrose concentration was 50% (w/w). The fractionation was carried out at least once, and the results were confirmed by repeating the experiments at least one other occasion. The n values (or the numbers of observations) indicate the numbers of liposome preparations reconstituted and assayed separately, or the numbers of aliquots of fat cell suspensions. The n values in Fig. 4 and Table 1 represent the numbers of separate experiments that were repeated with different batches of fat cells.

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Protein was assayed by the Bradford method (13; 5'-nucleotide

by the method of Avruch and Wallach (14), but in the presence of 1% Triton X-100 as described previously (13); NADH dehydrogenase (NADH:ferricyanide oxidoreductase) by the spectrophotometric method (16); UDP-galactose-N-acetylglucosamine galactosyltransferase, by the method of Plescher (17) as modified by Kono et al. (2); and the amount of fat cells by the malate dehydrogenase method as described in our previous studies (7, 10).

As is well known, various physiological parameters of fat cells are significantly different from batch to batch of cell preparations. Therefore, all the tests to be compared were carried out with aliquots of a pooled cell preparation, and a representative set of data obtained in a single experiment is presented in Figs. 1, 2, and 5 through 7. In Fig. 3 and Table II two almost identical sets of data are combined. The results reported in these figures and the table were confirmed by repeating the experiments at least on one other occasion. The n values (or the numbers of observations) indicate the numbers of liposome preparations reconstituted and assayed separately, or the numbers of aliquots of fat cell suspensions. The n values in Fig. 4 and Table 1 represent the numbers of separate experiments that were repeated with different batches of fat cells.
tidase activity (a marker of the plasma membrane) was almost exclusively localized in the plasma membrane-rich fraction (Fractions 3-7). In contrast, the UDP galactose:N-acetylgalactosamine galactosyltransferase activity (a marker of the Golgi apparatus in liver) formed not only a large peak in the Golgi-rich fraction (Fractions 13-17) but also a distinct peak in the plasma membrane-rich fraction. The NADH dehydrogenase activity (often regarded as a marker of the endoplasmic reticulum) formed three peaks in Fig. 1A. The first peak coincided with the peak of 5'-nucleotidase, the second peak roughly corresponded to a broad peak of protein (Fractions 10-14 in B) which was probably enriched with the endoplasmic reticulum, and the third small peak was found in the soluble fraction (Fraction 17). All of these NADH dehydrogenase activities were insensitive to 10 μM rotenone (data not shown) which is an inhibitor of mitochondrial NADH dehydrogenase (20). Mitochondria were pelleted at the bottom of the centrifuge tube in this sucrose density gradient centrifugation (data not shown). Insulin had no detectable effect on any of the above marker enzyme activities (data not shown).

For statistical evaluation of the results obtained by Methods A and B, we repeated the above fractionation experiments several times. The results as summarized in Table I indicate that the average insulin-dependent increase in the specific glucose transport activity (per mg of protein) observed in the plasma membrane-rich fraction was 4.6-fold by Method A and 6.3-fold by Method B. As considered later in detail (See “Discussion”), these values were considerably larger than those that were recorded in our previous experiments (1, 2). The average insulin-dependent increase in the total transport activity observed in the isolated plasma membrane-rich fraction was 61% of the activity decrease in the Golgi-rich fraction in Method A (4.32 ± 0.74 X 100), and 75% in Method B (5.05 ± 0.73 X 100). These results implied that the overall recovery of the plasma membrane-rich fraction was 61–75% of that of the Golgi-rich fraction. The recovery and enrichment of the plasma membranes from the fat cell homogenate were approximately 30% and 13-fold, respectively (data not shown), when estimations were made on the assumption that 5'-nucleotidase is the specific marker of the plasma membrane. Unfortunately, the corresponding values for the Golgi-rich fraction were unavailable for lack of any specific marker enzyme.

In the next set of experiments reported in Table II, we estimated what percentage of the glucose transport activity in the native plasma membrane was accounted for by the assay carried out in the reconstituted system. Since the uptake of n-glucose by fat cells cannot be measured directly, we determined the uptake of 3-O-methyl-n-glucose (a nonmetabolizable sugar) and 2-deoxy-n-glucose (which is accumulated in fat cells as its 6-phosphate and in liposomes as the free sugar) both in the intact fat cell system and in the reconstituted liposome system. We also measured the 5'-nucleotidase activity in the cell suspension and in the plasma membrane-rich fraction just prior to the sodium cholate solubilization and calculated the glucose transport activity relative to the 5'-

![Graph](http://www.jbc.org/)

**TABLE I**

Statistics of insulin effects on the protein concentrations and glucose transport activities observed in the pooled plasma membrane-rich and Golgi-rich fractions prepared by Methods A and B

|               | Protein | Glucose transport activity |
|---------------|---------|-----------------------------|
|               | μg/fraction | nmol/min/mg protein | nmol/min/fraction |
| **Method A (n = 8)** |         |                            |                  |
| Plasma membrane-rich fraction |         |                            |                  |
| No insulin    | 234 ± 18* | 5.42 ± 0.60*               | 1.27*            |
| +Insulin      | 225 ± 17 | 24.84 ± 0.90               | 5.59             |
| Insulin effect| None     | ×4.58 ± 0.85*              | 4.32             |
| Golgi-rich fraction |         |                            |                  |
| No insulin    | 221 ± 15 | 76.50 ± 4.88               | 16.91            |
| +Insulin      | 230 ± 20 | 42.75 ± 2.97               | 9.83             |
| Insulin effect| None     | ×0.56 ± 0.04*              | -7.08            |
| **Method B (n = 6)** |         |                            |                  |
| Plasma membrane-rich fraction |         |                            |                  |
| No insulin    | 218 ± 17 | 4.23 ± 0.24                | 0.99             |
| +Insulin      | 226 ± 19 | 26.43 ± 0.88               | 5.97             |
| Insulin effect| None     | ×6.25 ± 0.37*              | 6.05             |
| Golgi-rich fraction |         |                            |                  |
| No insulin    | 206 ± 19 | 80.61 ± 3.36               | 16.61            |
| +Insulin      | 212 ± 15 | 46.59 ± 3.00               | 9.88             |
| Insulin effect| None     | ×0.58 ± 0.04*              | -6.73            |

* Mean value ± S.E. (n, as indicated).

a Calculated from each pair of insulin experiments.
TABLE II

Efficiency of reconstitution of the glucose transport activity

| 3-O-methyl-D-glucose | No insulin | +Insulin | Insulin effect | Efficiency |
|----------------------|------------|----------|----------------|------------|
| In liposomes         | 0.12 ± 0.02’ | 0.36 ± 0.02 | x8.6 | 34 |
| In fat cells         | 0.75 ± 0.03 | 2.92 ± 0.08 | x8.3 | 26 |

The data in Fig. 5 indicate that the effects of hydrogen peroxide on the glucose transport activity in both plasma membrane-rich and Golgi-rich fractions were entirely unaffected when the cellular insulin receptor was modified by exposure of cells to trypsin at 1 mg/ml for 15 min (5, 25). As expected, the effects of insulin were completely abolished under the given conditions.

DISCUSSION

The results presented above in Tables I and II and Figs. 1 and 2 show that when the plasma membrane-rich fraction is prepared under conditions that would minimize cross-contamination by the Golgi-rich fraction, the insulin-dependent increase in the glucose transport activity observed in the former fraction is increased from the previously recorded level of 2.0- to 2.5-fold to 6.3-fold in Table I and to 6.3- and 8.6-fold in Table II. In the studies of insulin action, this increase is substantial. As mentioned earlier, the hormone routinely stimulates glucose transport in intact fat cells 5- to 10-fold. This should be noted, however, that there is no experimental evidence to indicate that the plasma membrane-rich fraction isolated in our present study is entirely free from contamination by the Golgi-rich fraction. If it were assumed that the fraction purified by Method B is still contaminated by 2% of the Golgi-rich fraction on the average, the "true" insulin effect could be roughly calculated from the data in Table I (Method B, last column) to be 9.8-fold (= (5.97 - 0.20) / (0.92 - 0.33)). This calculated level of hormone effect is approximately equal to that observed in the experiment presented in Fig. 2. Also, the calculated "true" effect is roughly comparable to the maximum insulin effect observed in our present study on the glucose transport activity in intact fat cells (Table II). A possible minor contamination of the isolated plasma membrane-rich fraction by the Golgi-rich fraction may also explain why the apparent reconstitution efficiency of the no insulin (or basal) transport activity appears to be slightly higher than that of the plus insulin activity (Table II).

Previously, attempts were made in this laboratory to calculate the "true" level of insulin effect from the observed value. However, these previous efforts were futile since, according to our view, UDP galactose:N-acetylgalactosamine galactosyltransferase is not a specific marker of the transport activity in the Golgi-rich fraction in fat cells (2). This view is supported by our present data which indicate that 15-20% of the transferase activity forms a distinct peak in the plasma membrane-rich fraction (Figs. 1 and 2). Cushman and Wardzala (5) estimated the "true" level of insulin effect from their cytochalasin B-binding data (their observed effect was 3.1-fold) on the assumption that a certain fraction of the NADH dehydrogenase activity could be used as a marker of the glucose transport activity in the intracellular storage site.

Effects of Agents That Have Insulin-like Activities—We next examined effects of agents that are known to have insulin-like effects on the glucose transport activity in intact fat cells. The agents tested were: hydrogen peroxide (21), sodium vanadate (22), trypsin (15-15-s treatment (23)), and p-chloromercuriphenyl sulphonate (24). As shown in Fig. 3, all these agents showed increased glucose transport activity in the plasma membrane-rich fraction, but also decreased the activity in the Golgi-rich fraction. Significantly, the agents that had weak activities in the plasma membrane-rich fraction also showed weak activities in the Golgi-rich fraction. The effects of the above four agents on the uptake of 3-O-methyl-D-glucose by intact fat cells are shown in Fig. 4. Although different cell preparations were used in these two experiments (Figs. 3 and 4), the results were similar, with a possible variance in the relative effects of trypsin and p-chloromercuriphenyl sulphonate.
FIG. 3 (left). Effects of agents that have insulin-like activities, as observed in the reconstituted system. Aliquots of pooled fat cells were exposed to: (a) buffer only (none), (b) 1 nM insulin for 10 min, (c) 100 mM hydrogen peroxide for 10 min, (d) 1 mM sodium vanadate (V03) for 30 min, (e) 1 mg/ml of trypsin for 15 s, or (f) 1 mM p-chloromercuriphenyl sulfonate (PCM) for 30 min, all at 37 °C. The trypsin treatment was terminated by the addition of 1 mg/ml of soybean trypsin inhibitor, and the incubation continued for an additional 15 min at 37 °C, as described earlier (23). Subsequently, cells were washed, homogenized, and fractionated by Method B. The glucose transport activity was determined in the reconstituted liposome system, and the results are shown as nanomoles of D-glucose taken up by liposomes per mg of protein, as determined at 20 s of incubation. The figure presents mean values ± standard errors of four experiments; n = 8. PM, plasma membrane.

FIG. 4 (center). Effects of agents that have insulin-like activities, as observed on 3-O-methyl-D-glucose uptake by intact fat cells. Aliquots of pooled fat cells were treated with various agents as described in Fig. 3. The uptake of 3-O-methyl-D-glucose (3-0-MG) was determined by the oil-flotation method. The figure presents mean values ± standard errors of means (n = 4).

FIG. 5 (right). Effects of proteolytic modification of the cellular insulin receptor. Aliquots of a pooled fat cell preparation were exposed to 1 mg/ml of trypsin for 15 min at 37 °C, and the action of trypsin was terminated by the addition of 1 mg/ml of soybean trypsin inhibitor, as previously described (25). Both control and trypsin-treated cells were then exposed to 1 nM insulin or 10 mM hydrogen peroxide for 10 min, homogenized, and fractionated by Method B. The glucose transport activities were determined as in Fig. 3. The figure presents results of a single set of experiments; n (see Fig. 3) = 4.

However, our present data indicate that NADH dehydrogenase is not an appropriate marker of the transport activity in the Golgi-rich fraction (Figs. 1 and 2), Carter-Su and Czech (26), on the other hand, observed a large insulin effect in the glucose transport activity reconstituted from the plasma membrane fraction (5- to 8-fold). However, since they failed to detect any significant insulin effect on the transport activity in the microsomal fraction, their data did not support the translocation hypothesis. Therefore, our data presented in Figs. 1 and 2 and Tables I and II appear to be the first experimental evidence which supports the view that the effect of insulin on glucose transport in fat cells may be largely, if not entirely, accounted for by the translocation mechanism.

The question whether the insulin effect on the glucose transport activity in intact fat cells can be quantitatively accounted for by the translocation mechanism is difficult to answer for two reasons. First, the so-called basal glucose transport activity in fat cells is significantly different from batch to batch of cell preparations and, as first noted by Winegrad and Renold (27), the activity is easily altered by a number of factors. Second, the so-called basal transport activity observed under "optimum" conditions is so small that it is difficult to estimate reliably, especially in the reconstituted system (Figs. 1 and 2 and Tables I and II). The view that fat cells have a minimum glucose transport activity in the absence of insulin is consistent with their metabolic function: under fed conditions (in the presence of insulin) these cells take up and convert glucose into fat whereas under starved conditions (in the absence of insulin) they hydrolyze the accumulated fat to supply nutrients to a number of cell types presumably including themselves; no glucose is required for this lipolytic reaction (28).

As discussed previously (8), the glucose transport assay performed in the reconstituted liposome system is highly reproducible, and the estimated transport activities are proportional to the concentrations of the membrane protein within a certain limit of the experimental error (8). In addition, our present data indicate that the glucose transport activity in the plasma membrane-rich fraction (either in the basal or
in the plus insulin state) can be solubilized, reconstituted, and assayed with an overall efficiency of approximately 25-35% (Table II). Therefore, it is suggested that the changes in the transport activity observed in the reconstituted system would indicate the actual changes in the transport activity induced in fat cells, e.g. by the effect of insulin.

Although the number of agents tested for their insulin-like effects is not very large, they include seemingly unrelated compounds: namely, hydrogen peroxide, sodium vanadate, trypsin, and p-chloromercuriphenyl sulfonate. Therefore, it is significant to note that (a) all of these agents stimulate glucose transport in fat cells apparently by inducing translocation of the glucose transport activity, and (b) none of them appears to stimulate the activity in the plasma membrane-rich fraction without lowering the activity in the Golgi-rich fraction. It is suggested, therefore, that the basal form of the plasma membrane is not associated with any significant number of glucose transport mechanisms that are stimulated by insulin or several other agents tested. Additionally, we found in our present study that hydrogen peroxide can induce the apparent translocation of the glucose transport activity in trypsin-treated fat cells that are insensitive to insulin (Fig. 5). We interpret this observation as indicating that neither the presence nor the internalization (15) of the intact insulin receptor is necessary for the translocation of the glucose transport activity.

Our time course data (Figs. 6 and 7), as well as those obtained by Karnieli et al. (4), are apparently consistent with the translocation hypothesis. In addition, we recently obtained preliminary data which suggest that the seemingly paradoxical temperature coefficient discussed in our previous communication (2) is caused by an insulin-like effect of low temperature and is actually consistent with the translocation hypothesis (29); a full paper on this subject is in preparation.

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