Specific Desensitization of Glycogen Synthase Activation by Insulin in 3T3-L1 Adipocytes

CONNECTION BETWEEN ENZYMATIC ACTIVATION AND SUBCELLULAR LOCALIZATION

Received for publication, June 6, 2000, and in revised form, September 25, 2000
Published, JBC Papers in Press, September 29, 2000, DOI 10.1074/jbc.M004902200

A protocol was developed in 3T3-L1 adipocytes that resulted in the specific desensitization of glycogen synthase activation by insulin. Cells were pretreated for 15 min with 100 nM insulin, and then recovered for 1.5 h in the absence of hormone. Subsequent basal and insulin-induced phosphorylation of the insulin receptor, IRS-1, MAPK, Akt kinase, and GSK-3 were similar in control and pretreated cells. Additionally, enhanced glucose transport and incorporation into lipid in response to insulin were unaffected. However, treatment reduced insulin-stimulated glycogen synthesis by over 50%, due to a nearly complete inhibition of glycogen synthase activation. Removal of extracellular glucose during the recovery period blocked the increase in glycogen levels, and restored insulin-induced glycogen synthase activation. Furthermore, incubation of pretreated 3T3-L1 adipocytes with glycogenolytic agents reversed the desensitization event. Separation of cellular lysates on sucrose gradients revealed that glycogen synthase was primarily located in the dense pellet fraction, with lesser amounts in the lighter fractions. Insulin induced glycogen synthase translocation from the lighter to the denser glycogen-containing fractions. Interestingly, insulin preferentially activated translocated enzyme while having little effect on the majority of glycogen synthase activity in the pellet fraction. In insulin-pretreated cells, glycogen synthase did not return to the lighter fractions during recovery, and thus did not move in response to the second insulin exposure. These results suggest that, in 3T3-L1 adipocytes, the translocation of glycogen synthase may be an important step in the regulation of glycogen synthesis by insulin. Furthermore, intracellular glycogen levels can regulate glycogen synthase activation, potentially through modulation of enzymatic localization.

Insulin stimulates glucose storage in peripheral tissues, through the coordinate modulation of glucose uptake and glycogen-metabolizing enzymes (1). The metabolic actions of this hormone arise from the utilization of compartmentalized signaling cascades, resulting in the activation of targeted pools of enzymes. Indeed, insulin differentially regulates signaling processes such as PI3K, which are also utilized by other growth factors (2, 3). In addition, insulin causes the intracellular movement of a variety of signaling components and effectors. Thus, the unique metabolic effects of insulin are mediated via the activation of compartmentalized enzymes and induction of protein translocation.

Glycogen synthase (GS) activity, the rate-limiting enzyme in glycogen synthesis, is controlled by a variety of mechanisms (4). The enzyme is phosphorylated on up to nine residues by several kinases, resulting in progressive inactivation. GS is also allosterically activated by glucose-6-phosphate (G6P), which overrides inhibition caused by phosphorylation. Furthermore, G6P binding to GS induces a conformational change, increasing its susceptibility to dephosphorylation (5, 6). Finally, elevation of intracellular glucose metabolites induces the translocation of cytosolic GS to glycogen-containing fractions in primary hepatocytes and 3T3-L1 adipocytes (7–9). Thus, GS activity can be increased through dephosphorylation, translocation, and allosteric activation. Insulin utilizes all three mechanisms to stimulate GS, via the synergistic elevation of glucose uptake and modulation of regulatory enzymes (1, 10, 11).

The precise signaling pathways used by insulin to activate GS remain unclear. Insulin-mediated dephosphorylation of GS may involve both kinase inhibition and phosphatase activation (10). Glycogen synthase kinase-3 (GSK-3), an upstream inhibitor of GS, is inactivated by insulin in a variety of cell lines and tissues (13–15). Additionally, GS is an excellent in vitro substrate for protein phosphatase-1 (PP1), which is activated by insulin (16–19). However, the relative contribution of GSK-3 inhibition versus phosphatase activation in the insulin-mediated activation of GS is controversial, and may vary between tissue and cell types. The coordinate stimulation of glucose transport and GS activity by insulin suggests that common signaling pathways may be shared. Indeed, numerous studies have implicated PI3K as a critical step in both insulin-stimulated GLUT4 vesicle translocation (reviewed in Ref. 20) and GS activation (21–23). However, other signaling pathways must be involved, because PI3K activation by other stimuli is not sufficient to replicate the unique effects of insulin on glucose metabolism (24–26).

Intracellular glycogen levels also exert a powerful regulatory effect over glucose transport and GS activity (reviewed in Ref. 27). Following a strenuous bout of glycogen-depleting exercise, basal GLUT4 translocation and GS activation in skeletal muscle are markedly increased. Insulin-stimulated glucose uptake...
and storage in glycogen-depleted muscle is also enhanced until glycogen stores are replenished. Conversely, superaccumulation of glycogen following exercise and refeeding inhibits further glycogen metabolism, due to reduced GLUT4 translocation and GS activation by insulin or contraction (28–30). However, the mechanisms by which glycogen levels feedback to regulate glucose transport and glycogen metabolism are unknown.

In type II diabetic patients, insulin loses its ability to promote glucose uptake and storage, resulting in chronic fasting hyperglycemia. Although insulin metabolic signaling can be experimentally inhibited by a variety of agents and conditions (31–38), the precise molecular abnormalities that cause insulin resistance in vivo remain unclear. In the present study we have identified a novel paradigm for the desensitization of glycogen synthase activation in 3T3-L1 adipocytes. Insulin potently increases glucose transport, GS activity, and glycogen accumulation in these cells (18, 25, 39). However, acute insulin pretreatment markedly reduced subsequent stimulation of glycogen synthesis, without affecting immediate insulin receptor signaling or glucose uptake. Rather, insulin pretreatment increased glycogen levels, altered the intracellular distribution of GS, and specifically blocked enzymatic translocation and activation. These results indicate that intracellular glycogen levels may impinge on insulin-mediated GS activation through regulation of enzymatic localization.

**EXPERIMENTAL PROCEDURES**

**Materials—**All cell culture reagents were purchased from Life Technologies, Inc., with the exception of sera, which was obtained from Summit Biotechnology ( Ft. Collins, CO). Insulin, 2-deoxyglucose, and differentiation agents were supplied by Sigma. UDP-(U-14C)glucose (308 mCi/mmol) was from by ICN, and n-[14C]glucose (3.4 mCi/mmol) and 2-deoxy-o-[14C]glucose (323 mCi/mmol) were obtained from PerkinElmer Life Sciences. Sources of antibodies: anti-glycogen synthase, the generous gift of Dr. J. Lawrence Jr. (University of Virginia); anti-phospho-AKT (serine 473) and anti-phospho-GSK-3 (serine 21/9), New England BioLabs; anti-phospho-MAPK, Promega; anti-phosphotyrosine, UBI and Transduction Laboratories; horseradish peroxidase-conjugated goat anti-rabbit and goat anti-mouse IgG, Bio-Rad; horseradish peroxidase-conjugated rabbit anti-chicken IgG, Accurate Chemical & Corp. (Westbury, NY). ECL reagent was purchased from Amersham Pharmacia Biotech, and GFA filters were supplied by Whatman.

Cell Culture and Experimental Treatment—3T3-L1 fibroblasts were maintained and differentiated as described (9). Adipocytes were used 6–14 days after completion of the differentiation protocol, when >90% of the cells expressed the adipocyte phenotype. Prior to experiments, cells were washed two times with low serum medium (Dulbecco's modified Eagle's medium containing 5 mM glucose, 0.5% fetal bovine serum, 16–18 h at 39,000 rpm in a SW40Ti rotor. 1-ml fractions were collected from the top of the gradient, and the pellet was resuspended in 1 ml of lysis buffer without detergent. Samples were then analyzed by immunoblotting or glycogen synthase activity assay as described (39). Protein determination was by Bradford.

**RESULTS**

**Insulin Pretreatment of 3T3-L1 Adipocytes Results in the Selective Inhibition of GS Activation—**An *in vitro* model for the desensitization of insulin-stimulated glycogen synthesis was established in 3T3-L1 adipocytes. Cells were pretreated for 15 min with 100 nM insulin, washed extensively, and then allowed to recover for 1.5 h (Fig. 1). The regulation of glycogen synthesis by insulin was then compared in naive and pretreated cells. Insulin caused a 100-fold increase in glucose incorporation into glycogen in control adipocytes (Fig. 2). However, insulin-mediated glycogen accumulation was markedly inhibited in the pretreated cells, due to an increase in basal rate, and a greater than 50% suppression of maximal insulin-stimulated glycogen synthesis rate (Fig. 2).

To initially characterize the site of impairment in insulin action, early signaling events were compared in control and desensitized 3T3-L1 adipocytes. Following pretreatment,
washed out, and recovery, the cells were incubated for 5–60 min with 100 nM insulin. Lysates were prepared, and the phosphorylation state of several proteins was measured by immunoblotting. The insulin-stimulated tyrosine phosphorylation of IRS-1 and the insulin receptor was distinguishable in the control and pretreated cells (Fig. 3A, IRS-1, IR). Furthermore, the basal phosphorylation of the proteins was identical in both sets of cells (Fig. 3A), indicating that the pretreated cells had recovered from the initial insulin stimulation. Similar results were obtained when the phosphorylation state of Akt and mitogen-activated protein kinases were measured (Fig. 3A, pAKT, pMAPK). The regulation of GSK-3 activity in both sets of cells was compared by immunoblotting and activity assay. As previously reported (41), insulin caused a rapid and sustained decrease in GSK-3 activity in 3T3-L1 adipocytes (Fig. 3B), which was unaffected in the pretreated cells (Fig. 3B). Similar results were obtained in anti-phospho-GSK-3 immunoblots (Fig. 3B, inset). These results demonstrate that several insulin-signaling cascades are unaffected by the pretreatment protocol.

The stimulation of glycogen synthesis by insulin is dependent on increased glucose uptake and phosphorylation, and activation of glycogen synthase. These parameters were next examined in naïve and pretreated cells. Following the initial insulin stimulation and recovery, rates of glucose transport and incorporation into lipid were measured. Insulin caused a similar increase in 2-deoxyglucose uptake in both sets of cells, although basal and insulin-stimulated glucose transport were slightly elevated in the pretreated cells (Fig. 4A). Interestingly, basal glucose incorporation into lipid was markedly elevated in the pretreated cells (Fig. 4B). However, pretreatment did not affect maximal insulin-stimulated glucose incorporation into lipid (Fig. 4B), indicating that glucose uptake and phosphorylation were not compromised. In contrast, a 15-min insulin stimulation caused a 4-fold increase in the GS activity ratio in control cells, but did not significantly elevate GS activity in the pretreated cells (Fig. 5A). Insulin did not increase GS activity for up to an hour in the pretreated cells (Fig. 5B), demonstrating that the desensitization event was not caused by delayed GS activation. Pretreatment had no effect on GS protein levels, measured by immunoblotting or enzymatic activity (Fig. 8A; data not shown). Therefore, the reduction in insulin-mediated glycogen accumulation in pretreated cells arises from an inability of the hormone to dephosphorylate GS. The residual stimulation of glycogen synthesis in the desensitized 3T3-L1 adipocytes may arise from the allosteric activation of GS by G6P and/or inhibition of glycogen phosphorylase activity by insulin.

Role of Glycogen Levels in the Regulation of GS Activity by Insulin—The potential role of glycogen accumulation in the desensitization of GS activation by insulin was investigated. Following pretreatment and washout, half of the wells were incubated in recovery medium lacking glucose. Removal of extracellular glucose blocked the 30% increase of intracellular glycogen levels during the recovery period (data not shown). Immediately prior to the second insulin stimulation, all wells were switched to medium containing 5 mM glucose. Insulin-stimulated GS activity and glycogen synthesis rates were reduced in pretreated cells that recovered in glucose-containing medium (Fig. 6, A and B). However, removal of extracellular glucose during recovery blocked desensitization, because insulin caused a comparable increase in GS activity (Fig. 6A) and glycogen synthesis (Fig. 6B) in both sets of cells.

Next, the effects of decreasing cellular glycogen content on reversing GS desensitization were investigated. After pretreatment and recovery, 3T3-L1 adipocytes were treated for 15 min with the glycogenolytic agent isoproterenol, washed extensively, and then allowed to recover for 1 h prior to insulin stimulation. Insulin-dependent phosphorylation of the insulin receptor, IRS-1, Akt kinase, and GSK-3 was unaffected by isoproterenol pretreatment (data not shown). Isoproterenol
lately restored the ability of insulin to stimulate GS activity (Fig. 7). Together, these results indicate that, in 3T3-L1 adipocytes, increased intracellular glycogen levels can specifically override the regulation of GS activity by insulin.

Insulin-induced Translocation and Activation of GS Is Blocked in Desensitized Cells—Insulin treatment of 3T3-L1 adipocytes results in the translocation of GS from the cytosol to glycogen-containing fractions (9). Enzymatic redistribution is dependent on insulin-stimulated glucose uptake and is likely mediated by increased UDP-glucose levels (9). The intracellular localization and activation state of GS were next examined using sucrose gradients. Following a 15-min incubation with 100 nM insulin, cells were washed, scraped into buffer, and lysed by sonication. 2 ml of cellular lysate was loaded onto a 10-ml continuous 15–80% sucrose gradient and centrifuged at 10,000 g for 45 min at 4 °C. The gradients were fractionated into 1-ml fractions, with the supernatant collected and the pellets retained. GS activity was measured in vitro using sucrose gradients. Following pretreatment and recovery as in A, half the wells were stimulated for 15 min with 100 nM insulin and allowed to recover for 1.5 h in the presence of 5 mM extracellular glucose. Cells were then stimulated for 15 min (A) or 5–60 min (B) in the absence and presence of 100 nM insulin and lysates were prepared. GS activity was measured in vitro in the absence and presence of 10 mM glucose-6-phosphate. Results are representative of six experiments (A) or the average of the means of three independent experiments (B).

Direct measurement of glycogen levels in the fractions was hindered by the presence of sucrose. However, glycogen sedimentation was determined indirectly, as amylase pretreatment (40 μg/ml for 15 min at 30 °C) of insulin-treated 3T3-L1 lysates prior to gradient loading resulted in a loss of GS immunoreactivity from fractions 9–12 and the pellet, and in a reappearance in fractions 4–7 (data not shown). These observations indicate that the cellular glycogen stores are located in fractions 9–12 and the pellet, and confirm that cytosolic GS is translocating to glycogen in response to insulin (9). In parallel, GS activity in the fractions was assayed in the absence and presence of 10 mM G6P, to measure active and total GS, respectively. The pellet fraction from control cells contained the majority of GS activity (Fig. 8B, +G6P; notice the large disparity in scales used between the pellet and other fractions). However, insulin treatment of control cells only slightly increased G6P-independent GS activity in the pellet fraction (Fig. 8B versus Fig. 8C, −G6P). In contrast, insulin caused a complete activation of GS in fractions 9–12 (Fig. 8C), which are enriched for translocated enzyme (compare +G6P, fractions 9–12, Fig. 8B versus Fig. 8C; also Fig. 8A, Con/Bas versus Con/Ins). These results suggest that translocated GS represents a disproportional amount of the insulin-stimulated enzymatic activity assayed in crude 3T3-L1 adipocyte lysates. In contrast, GS activity was not increased in any fraction from the desensitized cells (data not shown), indicating that proper basal localization of GS may be important for enzymatic activation by insulin.
DISCUSSION

Although a considerable understanding of the physiological effects of insulin exists, the exact molecular mechanisms underlying insulin action have remained relatively elusive despite years of extensive investigation. A vital step in this proc-

FIG. 6. Removal of extracellular glucose during recovery blocks desensitization. Following a 1.5-h serum starvation, 3T3-L1 adipocytes were pretreated in the absence (Con) and presence (Pre) of 100 nM insulin for 15 min. Cells were washed extensively, and placed in low serum medium containing 0 or 5 mM glucose for 1.5 h. All wells were switched to low serum medium containing 5 mM glucose immediately prior to the second, 15-min stimulation with 100 nM insulin. GS activity (A) or glycogen synthesis rate (B) was measured as described under “Experimental Procedures.” Con, control cells; Pre, pretreated cells; 0, recovery medium containing 0 mM glucose; 5, recovery medium containing 5 mM glucose. All results are representative of three to six independent experiments.

FIG. 7. Isoproterenol reverses the development of GS desensitization. 3T3-L1 adipocytes were pretreated as in Fig. 1 and recovered for 1 h in the presence of 5 mM glucose. Indicated wells were then treated for 15 min with 1 μM isoproterenol (IPT). Following washout and a 1-h recovery in low serum media with 5 mM glucose, cells were stimulated in the absence (Basal) and presence (Insulin) of 100 nM insulin, and glycogen synthase activity was measured as described under “Experimental Procedures.” Results are the average of the means from three independent experiments.

FIG. 8. Insulin differentially regulates GS activity and localization in control and desensitized cells. 150-mm plates of 3T3-L1 adipocytes were pretreated and allowed to recover for 1.5 h. Following a 15-min stimulation with 100 nM insulin, cells were collected in 2 ml of buffer. Cellular lysates were applied to the top of a 10-ml continuous 15–80% sucrose gradient and centrifuged for 16 h. 1-ml fractions were removed, and the pellet was resuspended in lysis buffer lacking Triton X-100. Fractions from control and desensitized cells were analyzed by anti-GS immunoblotting (A). Additionally, fractions from basal and insulin-treated control cells were assayed for GS activity (B and C). Note that the pellet fraction is plotted on a different scale; values for G6P-independent GS activity in the pellet have been indicated numerically to aid in comparison with other fractions. Fraction 1 corresponds to the top of the gradient. Cellular glycogen stores sedimented into fractions 9–12 and the pellet. Con, control cells; Pre, pretreated cells; Bas, basal; Ins, insulin-treated; G6P, glucose 6-phosphate. Results from control and desensitized cells in A are from two independent experiments. All results are representative of three independent experiments.
ess has involved defining the unique signaling pathways initiated by insulin through its receptor, which also utilizes downstream signaling molecules common to other growth factors. Spatial compartmentalization and subcellular translocation of signaling molecules are emerging concepts that may help explain insulin action. Insulin activates targeted pools of enzymes and recruits specific signaling components to particular intracellular locales, allowing molecular events conducive to its own unique signal to occur in relative isolation from other signaling pathways.

Of obvious physiological relevance, the inability of certain tissues to respond appropriately to insulin results in a variety of syndromes known collectively as diabetes mellitus. The most commonly occurring diabetic syndrome, type II diabetes, is characterized and is in fact preceded by the development of insulin resistance in peripheral tissues. Numerous reports have described experimental paradigms for the development of insulin resistance in both in vitro and in vivo. Elevation of extracellular glucose or insulin levels has been shown to inhibit insulin receptor signaling (31, 42). In addition, exposure of cells to specific agents such as phorbol esters, tumor necrosis factor-α, okadaic acid, and glucosamine also inhibit metabolic regulation by insulin (36–38, 43, 44). Previous reports have demonstrated that chronic insulin treatment of 3T3-L1 adipocytes blocked subsequent insulin-stimulated glucose transport due to a reduction in GLUT4 expression and/or translocation (32, 45–47). However, in these experiments, cells were exposed to insulin for 6–12 h to achieve maximal effects. In the present study, an acute 15-min pretreatment with 100 nM insulin, followed by a 1.5-h recovery in the absence of hormone, was sufficient to make GS refractory to a second insulin treatment (Fig. 5). All other insulin-signaling parameters measured were largely unaffected, including insulin receptor phosphorylation, GSK-3 inactivation, and stimulation of glucose transport (Figs. 3 and 4). Together these observations in 3T3-L1 adipocytes mirror previous reports of the development of insulin resistance in denervated muscle, where inhibition of insulin-stimulated GS activation temporally preceded inhibition of glucose transport (33). The inhibition of GS activation by insulin in denervated muscles (33, 34) stemmed from an inability to promote enzymatic dephosphorylation (48), despite normal initial insulin-mediated glucose uptake (33). However, the mechanisms by which denervation inhibits insulin signaling in muscle are still unknown.

A connection between intracellular glycogen levels and rates of glucose uptake and storage has been elucidated via exercise studies (reviewed in Ref. 27). Glycogen depletion in skeletal muscle caused by intense bouts of exercise has been shown to result in transient increases in both basal glucose uptake and glycogen synthase activity (49, 50). Additionally, the sensitivity of glycogen-depleted muscle cells to insulin remains elevated until glycogen levels have been replenished. Furthermore, contraction-stimulated GS activity is refractory to inhibition by cAMP elevation (51). Thus, glycogen synthesis is elevated by several mechanisms until glycogen stores are replenished. Conversely, increased skeletal muscle glycogen levels in humans, achieved through exercise and refeeding, was shown to directly inhibit GS activation by insulin (30). Despite a 2-fold increase in G6P levels, GS activity was reduced by 30%, resulting in shunting of glucose from glycogen storage to oxidative pathways (30). Recently, Montell et al. (52) varied glycogen levels in cultured human muscle cells, through adenosyl-mediated overexpression of glycogen phosphorylase and manipulation of extracellular glucose concentrations. After glycogen depletion, the initial temporal activation of GS by elevated extracellular glucose correlated with intracellular glycogen levels rather than with G6P levels (52). Cumulatively, these data demonstrate that glycogen levels can directly modulate glycogen synthase activity, even overriding hormonal and allosteric regulation. However, the molecular mechanisms by which intracellular glycogen levels can autoregulate glycogen metabolism remain unclear.

Insulin stimulation of glycogen synthase in peripheral tissues is mediated by the simultaneous increase of glucose transport and GS activity. Insulin treatment induces the translocation of GLUT4-containing vesicles to the plasma membrane, resulting in enhanced glucose uptake (reviewed in Refs. 20 and 53), which is essential for the full activation of GS by insulin (5, 9). In 3T3-L1 adipocytes, elevated UDP-glucose levels resulted in the translocation of cytosolic GS to glycogen-containing fractions (9). It is tempting to speculate that UDP-glucose might cause GS to bind to the ends of the glycogen chains, where the enzyme could more efficiently catalyze UDP-glucose incorporation into glycogen. Interestingly, insulin was observed to preferentially activate GS in fractions enriched for translocated enzyme while having little effect on the majority of GS activity present in the dense pellet fraction (Fig. 8C). Consequently, a minority of total cellular GS activity would appear to be responsible for most of the newly synthesized glycogen. In contrast, an acute insulin pretreatment of 3T3-L1 adipocytes resulted in a 30% increase in glycogen levels and the stable localization of GS in the denser intracellular fractions. Subsequently, insulin was unable to induce GS translocation, which correlated with the inhibition of enzymatic activation. These results indicate that, in 3T3-L1 adipocytes, the translocation of cytosolic GS to denser, glycogen-containing fractions may play an important role in the regulation of GS activity and glycogen synthesis by insulin.

Insulin stimulates GS activity by promoting enzymatic dephosphorylation. Both the activation of PP1 and the inactivation of GSK-3 have been proposed to mediate this insulin effect (12). Additionally, increased glucose uptake synergistically augments GS activation by insulin in a variety of cell models, by enhancing PP1-mediated dephosphorylation (5, 9, 54). In the desensitized 3T3-L1 adipocytes, insulin was unable to promote GS activation, despite normal insulin-stimulated glucose uptake and phosphorylation of GSK-3. These results suggest that desensitization of GS may result from spatial separation of the enzyme from its insulin-mediated regulators. The potential activation of a GS kinase or the impairment of a distal insulin-signaling component in the desensitized cells cannot be excluded. However, acute reduction of intracellular glycogen levels, achieved by either incubation of cells in glucose-free medium or addition of glycogenolytic agents, blocked the development of GS desensitization (Figs. 6 and 7). Thus, increased glycogen levels may act in a feedback fashion to inhibit insulin-mediated dephosphorylation and activation of GS, through regulation of GS intracellular localization.

In summary, insulin induces the translocation of cytosolic GS to the glycogen-containing fractions in 3T3-L1 adipocytes. The translocated enzyme is preferentially activated by insulin, and thus represents a disproportionate amount of GS activity mediating glycogen synthesis. Subsequent glycogen accumulation may result in the trapping of GS within the denser glycogen polymers, resulting in a spatial uncoupling of GS from its insulin-sensitive activators. Conversely, as glycogen levels are depleted, GS would be released back into the cytosol, priming it for activation by insulin. This potential mechanism allows for a sensitive, bidirectional modulation of GS activation by cellular glycogen levels. Experiments are underway to address the potential regulation of GS activity and localization by insulin and glycogen levels in skeletal muscle.
Acknowledgments—We thank Dr. C. Mastick for establishing conditions to simultaneously measure glucose incorporation into glycogen and lipid and Drs. C. Burant, P. Hansen, and A. Saltiel for helpful discussions.

REFERENCES

1. Brady, M. J., Pessin, J. E., and Saltiel, A. R. (1999) Trends Endocrinol. Metab. 10, 408–413
2. Moule, S. K., Edgell, N. J., Welsh, G. I., Diggle, T. A., Foulstone, E. J., and Shepherd, P. R. (1999) Biochem. J. 318, 55–60
3. Moule, S. K., Edgell, N. J., Welsh, G. I., Diggle, T. A., Foulstone, E. J., and Shepherd, P. R. (1999) Biochem. J. 318, 55–60
4. Moule, S. K., Edgell, N. J., Welsh, G. I., Diggle, T. A., Foulstone, E. J., and Shepherd, P. R. (1999) Biochem. J. 318, 55–60
5. Moule, S. K., Edgell, N. J., Welsh, G. I., Diggle, T. A., Foulstone, E. J., and Shepherd, P. R. (1999) Biochem. J. 318, 55–60
Specific Desensitization of Glycogen Synthase Activation by Insulin in 3T3-L1 Adipocytes: CONNECTION BETWEEN ENZYMATIC ACTIVATION AND SUBCELLULAR LOCALIZATION

Timothy C. Jensen, Sean M. Crosson, Pavna M. Kartha and Matthew J. Brady

J. Biol. Chem. 2000, 275:40148-40154.
doi: 10.1074/jbc.M004902200 originally published online September 29, 2000

Access the most updated version of this article at doi: 10.1074/jbc.M004902200

Alerts:
- When this article is cited
- When a correction for this article is posted

Click here to choose from all of JBC's e-mail alerts

This article cites 54 references, 32 of which can be accessed free at http://www.jbc.org/content/275/51/40148.full.html#ref-list-1