Overexpression of Protein Targeting to Glycogen in Cultured Human Muscle Cells Stimulates Glycogen Synthesis Independent of Glycogen and Glucose 6-Phosphate Levels*

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There is growing evidence that glycogen targeting subunits of protein phosphatase-1 play a critical role in regulation of glycogen metabolism. In the current study, we have investigated the effects of adenovirus-mediated overexpression of a specific glycogen targeting subunit known as protein targeting to glycogen (PTG) in cultured human muscle cells. PTG was overexpressed both in muscle cells cultured at high glucose (glycogen replete) or in cells incubated for 18 h in the absence of glucose and then incubated in high glucose (glycogen re-synthesizing). In both glycogen replete and glycogen resynthesizing cells, PTG overexpression caused glycogen to be synthesized at a linear rate 1–5 days after viral treatment, while in cells treated with a virus lacking a cDNA insert (control virus), glycogen content reached a plateau at day 1 with no further increase. In the glycogen replete PTG overexpressing cells, glycogen content was 20 times that in controls at day 5. Furthermore, in cells undergoing glycogen resynthesis, PTG overexpression caused a doubling of the initial rate of glycogen synthesis over the first 24 h relative to cells treated with control virus. In both sets of experiments, the effects of PTG on glycogen synthesis were correlated with a 2–3-fold increase in glycogen synthase activity state, with no changes in glycogen phosphorylase activity. The alterations in glycogen synthase activity were not accompanied by changes in the intracellular concentration of glucose 6-phosphate. We conclude that PTG overexpression activates glycogen synthesis in a glucose 6-phosphate-independent manner in human muscle cells while overriding glycogen-mediated inhibition. Our findings suggest that modulation of PTG expression in muscle may be a mechanism for enhancing muscle glucose disposal and improving glucose tolerance in diabetes.

Glycogen metabolism is regulated in part by a balance between glycogen synthase (GS) and glycogen phosphorylase (GP) activities. Both enzymes are known to be modified by phosphorylation-dephosphorylation reactions. Dephosphorylation of GS causes its activation, while GP becomes inactivated. Dephosphorylation of glycogen metabolizing enzymes has been mainly attributed to protein phosphatase 1 (PP1) activity (1). In support of this notion, PP1 is known to bind to the glycogen particle in muscle, and has also been shown to catalyze dephosphorylation of GS, GP, and phosphorylase kinase when assayed in vitro (2). However, less is known about the mechanisms that control the specific action of PP1 on glycogen metabolizing enzymes in the intact cell.

It is increasingly appreciated that the activity of PP1 is affected by proteins that bind to the enzyme and target it to specific intracellular sites. With regard to glycogen metabolism, a family of glycogen targeting subunits of PP1 have recently emerged. These proteins include GMI or RGl (3) which is expressed in skeletal muscle, Gl (4), expressed mainly in the liver, and PPP1R5 or protein targeting to glycogen (PTG) (5, 6) and PPP1R6 (7), which are expressed in a wide variety of tissues. PTG is present in muscle and liver and has been shown to interact with PP1, GS, phosphorylase kinase, and possibly, GP (8). Nevertheless, the metabolic impact of these protein/protein interactions is not fully understood, and has only been studied in a limited number of cell types. Previous studies of overexpression of PTG in fibroblasts (5), hepatocytes (9), or liver of intact animals (10) have demonstrated this protein causes clear activation of GS and potent stimulation of glycogen synthesis. In hepatocytes or intact liver, PTG overexpression also appears to impair glycogenolysis induced by fasting or glycogenolytic agents (9, 10). However, subsequent studies have shown that overexpression of the liver-specific isoform of glycogen targeting subunit, Gl, has an even larger activating effect on GS and glycogen synthesis than PTG (11), while allowing efficient activation of glycogenolysis in response to forskolin. Thus, distinct metabolic and regulatory effects of different glycogen targeting subunit isoforms are beginning to emerge. This raises the issue of whether cellular context also affects the metabolic impact of these proteins. The current study sought to gain insight into this issue via adenovirus-mediated overexpression of PTG in human muscle cells, and comparison of our findings with those obtained previously in isolated hepatocytes.

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‡‡ The abbreviations used are: GS, glycogen synthase; GP, glycogen phosphorylase; PP1, protein phosphatase 1; PTG, protein targeting to glycogen.
Stimulation of Muscle Glycogen Synthesis by PTG

Glycogen synthesis in muscle is maximally activated after glycogen-depleting exercise. This effect has been ascribed to the activation of GS triggered by exhaustion of glycogen stores (12–15), mediated in turn by release of the inhibitory action of glycogen on PP1 (16). Additionally, at elevated glycogen levels, it has been suggested that glucose-6-P plays an important regulatory role by binding to GS and rendering it a better substrate for protein phosphatases 1 and 2A (17). In support of these ideas, the increment in glucose-6-P caused by exposure of cells to glucose and insulin correlates with GS activity state (12, 18), whereas it negatively correlates with glycogen concentration (14, 19). Therefore, a second reason for overexpressing PTG in human muscle cells was to re-examine these concepts of regulation of glycogen metabolism in response to changes in glycogen targeting subunit expression.

EXPERIMENTAL PROCEDURES

Human Muscle Primary Cultures and Transduction with Adenovirus—Human muscle primary cultures were initiated from satellite cells of muscle biopsies obtained with informed consent and approval of the Human Studies Committee of the Hospital Sant Pau (Barcelona). Aneural muscle cultures were established in a monolayer according to the technique described by Askanas et al. (20). Cultures were grown in Dulbecco’s modified Eagle’s medium (MEM) supplemented with 10% fetal bovine serum, 1% penicillin/streptomycin, 2 mM glutamine, and 1 mM phenylmethylsulfonyl fluoride and then sonicated. Immediately after myoblast fusion, medium was replaced by a medium devoid of fibroblast growth factor, epidermal growth factor, and glutamine. Muscle cultures were maintained in this medium for up to 2 weeks.

Recombinant adenovirus containing a 2.6-kilobase fragment of the mouse PTG cDNA including the entire coding region (AdCMV-PTG) has been described elsewhere (9). Control virus (AdControl) contained the expression cassette backbone with no insert. The recombinant viruses were amplified in 293 cells and viral stocks of 1 × 10^9 plaque forming units/ml were prepared in 10% fetal bovine serum/Dulbecco’s modified Eagle’s medium as described (21). Gene delivery to muscle cultures was achieved by exposing 12-day-old fibers, induced to fuse by exposure, as indicated under “Results” and Figure legends.

Immunoblot Analysis—Cell monolayers were scraped into 100 μl of homogenization buffer consisting of 10 mM Tris-HCl (pH 7.0), 150 mM KF, 15 mM EDTA, 600 mM sucrose, 10 μg/ml leupeptin, 1 mM benzamidine, and 1 mM phenylmethylsulfonyl fluoride and then sonicated. Protein concentration was measured by the Bio-Rad protein assay reagent. Immunoblot analysis was performed with a polyclonal antibody raised against the amino terminus of PTG (Santa Cruz Biotechnology, Inc.). Detection of the primary antibody was accomplished using Lumi-Light Western blotting Substrate (Roche Molecular Biochemicals).

Enzyme Activity Assays—To measure GS and GP activities, 100 μl of homogenization buffer consisting of 10 mM Tris-HCl (pH 7.0), 150 mM KF, 15 mM EDTA, 600 mM sucrose, 15 mM 2-mercaptoethanol, 10 μg/ml leupeptin, 1 mM benzamidine, and 1 mM phenylmethylsulfonyl fluoride was used in order to scrape frozen plates containing the cell monolayers prior to sonication. The resulting homogenates were used for the determination of enzyme activities. GP activity was determined by the incorporation of [U-14C]glucose 1-phosphate into glycogen in the absence or presence of the allosteric activator AMP (5 mM) (22). GP activity was measured in the absence or presence of 10 mM glucose-6-P as described (23).

Metabolite Determinations—To measure glycogen content, cell monolayers were scraped into 100 μl of 30% KOH and the homogenates were boiled for 15 min. An aliquot of the homogenates was used for the measurement of protein concentration. Homogenates were spotted onto Whatman DE81 paper and glycogen was precipitated by protein precipitation papers in ice-cold 66% ethanol. Dried papers containing precipitated glycogen were incubated in 0.4 M acetate buffer (pH 4.8) with 25 units/ml of a-amylglucosidase (Sigma) for 90 min at 37°C. Glucose released from glycogen was measured enzymatically in a Cobas Fara II autoanalyzer with a GlucoQuant (Roche Molecular Biochemicals) kit. Glucose 6-phosphate concentration was measured enzymatically in neutralized HClO4 extracts using a Cobas Fara II autoanalyzer.

Impact of PTG Overexpression on Glycogen Synthesis and GS in Glycogen Replete Cells—Treatment of human muscle cells with the AdCMV-PTG adenovirus resulted in a clear time-dependent overexpression of mouse PTG as assessed by immunoblot analysis (Fig. 1), that was already detectable 1 day after viral treatment, with continued increases in expression observed through day 5.

In a first set of experiments, cells were preincubated at high glucose and insulin for a period of 12 days, which resulted in saturation of glycogen synthesis. At this point, cells were deprived of insulin and treated with AdCMV-PTG or a control virus. Glycogen levels increased in AdCMV-PTG-treated cells progressively with time after viral treatment for 5 days (Fig. 2A), and in parallel, media glucose clearance was enhanced compared with control cells (data not shown). At the end of this experiment (day 5), glycogen content was 20-fold higher in AdCMV-PTG-treated cells compared with cells treated with control virus. GS activity ratio was monitored during this same period (Fig. 2B). A persistent activation of GS was shown in PTG-overexpressing cells which was already maximal (3-fold increase) 24 h after viral treatment, suggesting a saturation of the PTG effect, since PTG expression continued to increase over the entire course of the 5 day experiment (see Fig. 1). Total GS activity in whole extracts was unaltered in AdCMV-PTG-treated cells (13.2 ± 0.7 milliunits/mg of protein) compared with controls (12.6 ± 1.3 milliunits/mg of protein).

Impact of PTG on Glycogen Resynthesis—In a second set of experiments, the effect of PTG on glycogen resynthesis was examined. To achieve this, muscle cells were treated with AdCMV-PTG or control virus and incubated in medium lacking glucose for 18 h to prevent accumulation of glycogen in PTG-overexpressing cells. Thereafter, cells were reincubated with 25 mM glucose. At the time of switching from glucose-deprived glucose to glucose containing medium, glycogen levels were identical in control and AdCMV-PTG-treated cells (Fig. 3A). However, GS activity ratio was approximately doubled in glucose-deprived AdCMV-PTG-treated cells relative to controls (Fig. 3B). After incubation with glucose, glycogen content increased in both cell types over a 24-h period, but at a higher rate in PTG-overexpressing cells. At 24 h, glycogen accumulation had reached a plateau in controls cells whereas it was still in a linear phase in PTG-overexpressing cells. At 24 h, PTG overexpressing cells had accumulated 4-fold more glycogen than controls. GS activity ratio was transiently increased by glucose in both groups of cells, but was higher throughout the course of the experiment in AdCMV-PTG-treated cells because of the higher basal value.

In a third set of experiments, we examined the glucose concentration dependence of the PTG effect on glycogen synthesis. After 18 h of glucose deprivation, cells were incubated with varying glucose concentrations, from 0.5 to 25 mM (Fig. 4). As described previously, maximal glycogen accumulation was achieved at a glucose concentration of 5 mM in control cells.
Glycogen accumulation was higher in PTG-overexpressing cells at all glucose concentrations tested, but no modification in the glucose concentration dependence was found. This is consistent with the fact that the glucose concentration dependence of glycogen accumulation in muscle cells depends on the kinetics of hexokinase II (24).

Glucose-6-P Accumulation and Glucose Uptake—We next determined the impact of PTG overexpression on glucose uptake and glucose-6-P levels in muscle cells. To accomplish this, cells were treated with AdCMV-PTG or control virus and then switched to a glucose-deprived medium for 18 h. Glucose-6-P levels were measured in cells after incubation with medium containing 25 mM glucose for varying time periods (Fig. 5). At the time of switching from glucose-deprived to glucose-containing medium, glucose-6-P levels were identical in control and AdCMV-PTG-treated cells. Glucose-6-P levels increased rapidly (about 6-fold) after glucose repletion, reaching a maximal level within 10 min, with no differences between control and PTG-overexpressing cells studied out to 4 h. Glucose uptake was also similar in controls and AdCMV-PTG-treated cells regardless of whether they were incubated in the absence of glucose (152.3 ± 2 and 160.6 ± 5.1 nmol of 2-deoxyglucose/well, respectively) or in the presence of 25 mM glucose (80.1 ± 1.4 and 86.1 ± 4.6 nmol of 2-deoxyglucose/well, respectively), suggesting no change in glucose transport capacity. We have previously shown that the increased uptake of glucose observed in glycogen-deprived muscle cells is due to up-regulation of GLUT1 expression (25).

Effect of PTG on GP and Glycogenolysis—We also examined...
the effect of PTG overexpression on GP activity ratio under different metabolic conditions. Overexpression of PTG in glucose-deprived cells did not significantly modify GP activity ratio (0.57 ± 0.05 in PTG-overexpressing cells versus 0.60 ± 0.07 in controls). GP activity ratios were also similar following 1 h of glucose reincubation of the two cell groups (0.53 ± 0.02 in PTG-overexpressing cells compared with 0.55 ± 0.02 in controls). Finally, overexpression of PTG in glycogen-replete cells for 3 days in the presence of 25 mM glucose also did not affect GP activity ratio (0.60 ± 0.13 in PTG overexpressing cells versus 0.65 ± 0.1 in controls). When glycogenolysis was stimulated by glucose deprivation, a decline in glycogen content was found in both control and PTG-overexpressing cells (Fig. 6). While the percent decrease in glycogen content was lower in PTG-overexpressing cells, due to much higher initial levels, the estimated amount of glucose mobilized was about 2-fold higher in these cells than in controls. Consistent with this finding, the amount of lactate released to the medium was 35% higher in PTG-overexpressing cells than in controls (data not shown). GP activity ratio transiently increased in response to 1 h of glucose withdrawal in both groups of cells (0.76 ± 0.12 in PTG overexpressers versus 0.77 ± 0.02 in controls). Total GP activity was similar in PTG-overexpressing cells compared with controls during all of the foregoing metabolic manipulations (data not shown). In summary, the activation of glycogen synthesis induced by PTG expression in muscle cells appears not to be mediated by regulation of GP activity. Moreover, expression of PTG in muscle cells does not inhibit glycogenolysis, in contrast to what has been described in isolated hepatocytes (9) and intact liver (10).

**DISCUSSION**

In this study, we have examined the effects of altered expression of PTG on regulation of glycogen metabolism in primary cultured human muscle cells. These experiments were conducted under two different conditions, namely in cells in which net glycogen synthesis was saturated due to prolonged incubation at high glucose concentrations, and in cells depleted of glycogen due to glucose deprivation. Overexpression of PTG in glycogen replete cells incubated at high glucose caused resumption of glycogen synthesis at a linear rate for at least 5 days, in contrast to control cells, which did not increase glycogen content during this time period. In glycogen-depleted cells, the overexpression of PTG also increased the rate of glycogen synthesis after glucose repletion compared with controls. In both situations, the effect of PTG on glycogen synthesis was correlated with activation of GS, but not with any change in GP activity.

In muscle, GS is thought to be activated by glycogen depletion (12–15), via release of an inhibitory effect of glycogen on PP1 (16), and by transient increments in glucose-6-P resulting from insulin and glucose stimulation (26). The current study demonstrates that these modes of regulation of GS activity are not required for activation of glycogen synthesis in muscle in response to PTG overexpression. Thus, overexpression of PTG increased the activity ratio of GS regardless of whether cells were depleted or loaded with glycogen. These data suggest that PTG is able to overcome the inhibitory effect of glycogen on PP1 activity. In addition, activation of GS was not related to increased glucose transport rates or intracellular glucose-6-P levels in PTG-overexpressing muscle cells compared with controls. Furthermore, the glucose concentration dependence of glycogen accumulation was unaltered in cells treated with AdCMV-PTG. Thus, while glycogen content was higher at each glucose concentration studied in PTG overexpressing cells, as expected in light of the higher GS activity ratio, glycogen accumulation became maximal at 5 mM glucose in both groups of cells, supporting a key regulatory role for the hexokinase reaction rather than GS in control of the glucose dependence of glycogen synthesis in muscle cells (24).

It should also be noted that the effect of PTG to activate GS was limited, with the maximal activity ratio attained in the presence of overexpressed PTG of 0.3. In a recent study comparing the effects of overexpressed PTG, Gm, and Gs in isolated hepatocytes, a similar saturating effect of PTG overexpression on GS activation was noted, while overexpression of Gs resulted in GS activity ratios of up to 0.7 (11). These observations might be explained by the fact that GS can be phosphorylated at multiple sites, with differential impacts on enzyme activity. In this context, our results could be interpreted to mean that PTG mediates the dephosphorylation of a subset of these sites, while Gs may promote more complete dephosphorylation. In addition, it is possible that besides PP1, type 2 phosphatases could contribute to the activation of the enzyme within muscle cells, as has been shown in tissue extracts (1, 17). Nevertheless, the partial activation of GS induced by PTG overexpression is
sufficient to stimulate glycogen synthesis in muscle cells over a period of at least 5 days.

The impact of PTG overexpression on GP was also examined. In contrast to GS, GP activity ratio was only slightly decreased by the overexpression of PTG, both in glycogen-depleted and glycogen-replete cells. This suggests that the PTG-induced increment in glycogen synthesis is solely due to the activation of the synthetic enzyme rather than inactivation of the enzyme responsible for glycogen degradation. Therefore, even though muscle GP a has been shown to form complexes with PTG in vitro (8), our data indicates that PTG does not seem to be crucial to the inactivation/dephosphorylation of GP by PP1 within muscle cells. This finding may be related to what has been described for G_L, which shows distinct PP1-binding sites that enhance dephosphorylation of GP and GS in an independent fashion (27). If a similar mode of regulation exists in PTG, it could be reflected in different binding affinities for GS and GP.

Tissue-specific metabolic effects of PTG overexpression emerge from comparison of the results of the current study in muscle cells with those of previous studies in hepatocytes (9) or intact liver (10). For example, PTG overexpression in muscle does not cause glycogen accumulation in the absence of glucose, whereas large amounts of glycogen are synthesized in the absence of glucose in isolated hepatocytes. Presumably, this stems from the fact that muscle cells lack expression of key glucogenic enzymes that are required for the indirect pathway of glycogen synthesis that take place in hepatocytes. In addition, GP and glycogenolysis are activated in an apparently normal fashion in response to glucose deprivation in PTG overexpressing muscle cells, while glycogenolytic responses to forskolin in intact hepatocytes (9), or to fasting in liver of intact animals (10), is clearly impaired by PTG overexpression. It has been suggested that among glycogen targeting subunit isoforms, G_M contains 2 serines that may be targets for phosphorylation in response to glycogenolytic agents, while G_L is regulated allosterically by binding of phosphorylase a to its COOH-terminal tail (28). Neither of these mechanisms appears to be operative in PTG (5, 8). The current study demonstrates that tissue context is another, heretofore unappreciated, factor in regulation of the activity of glycogen targeting subunits. The specific factors that allow normal regulation of glycogenolysis in the context of a PTG overexpressing muscle cell, but not in a PTG overexpressing liver cell remain to be identified.

The implication of our data is that an increase in PTG expression in muscle might constitute a means of activating GS and glycogen synthesis independent of glycogen content or glucose-6-P levels, with possible therapeutic implications for lowering of blood glucose levels in diabetes. Nevertheless, extrapolation of our findings to the in vivo condition should be undertaken with caution, based on our demonstration that glucose transport is not limiting in cultured human muscle due to very high levels of GLUT1 (25). In intact muscle in situ, GLUT-4-mediated glucose transport may exert a rate-limiting effect. It will therefore be necessary to test directly whether PTG overexpression and GS activation in muscle is sufficient to enhance muscle glucose disposal in vivo. This may be achieved in future studies in transgenic mice, or by direct injection of AdCMV-PTG into muscle of neonatal rats, as we have demonstrated for an adenovirus containing the glucokinase cDNA (29). Additionally, it remains to be determined whether PTG content varies in muscle cells under different physiological conditions. Our clear finding that overexpression of PTG causes a persistent activation of GS independent of glycogen and glucose-6-P levels in human muscle cells provides impetus for further investigation of these issues.

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