Cardiac glycogen accumulation after dexamethasone is regulated by AMPK

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Glycogen is an immediate source of glucose for cardiac tissue to maintain its metabolic homeostasis (3). However, its excess has been suggested to bring about structural and physiological impairments including an ionic imbalance, a change in pH, and stimulation of pathways leading to hypertrophic signaling. Thus, glycogen accumulation that is associated with mutation of 5′-AMP-activated protein kinase (AMPK) has been reported to cause cardiac hypertrophy, conduction system failure, and ventricular arrhythmias (1). In glycogen storage diseases like Pompe disease, characterized by deficiency of debranching enzyme function, an excessive accumulation of cardiac glycogen leads to left ventricular hypertrophy and subsequent failure (55).

Glucocorticoids have widespread use as anti-inflammatory and immunosuppressive agents (47). However, both excess endogenous and exogenous glucocorticoids are known to contribute toward cardiovascular complications (39, 48). These cardiac abnormalities could be secondary to glucocorticoid-induced insulin resistance and type 2 diabetes and alterations in cardiac metabolism. With the latter, we have previously demonstrated that in hearts from dexamethasone (Dex)-treated animals, amplification of lipoprotein lipase provided the heart with excessive fatty acids that are known to induce cardiomyopathy (43, 53, 57). Glycogen accumulation was also enhanced in these hearts. We rationalized that this increase in glycogen was a consequence of compromised glucose oxidation observed in Dex-treated hearts (43). In the present study, we examined whether additional factors related to glycogen synthesis, such as glucose entry and GS, also play a role in the accumulation of this stored polysaccharide. Our data suggest that in the presence of intact insulin signaling, AMPK-mediated glucose entry combined with the activation of glycogen synthase and a reduction in glucose oxidation (Qi et al., Diabetes 53: 1790–1797, 2004) act together to promote glycogen storage. Should these effects persist chronically in the heart, they may explain the increased morbidity and mortality observed with long-term excesses in endogenous or exogenous glucocorticoids.

ON METABOLIC DEMAND, glycogen, a mobilized storage form of glucose, is readily broken down to yield glucose moieties. The major rate-limiting enzymes involved with the metabolism of glycogen include glycogen synthase (GS) and phosphorylase. The activity of these enzymes is regulated by both phosphorylation and allosteric stimulation (24).

MATERIALS AND METHODS

Experimental animals. This investigation conformed with the Guide for the Care and Use of Laboratory Animals (National Institutes of Health) and the University of British Columbia and was approved by the

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Fig. 1. Dexamethasone (Dex) effects on whole body and tissue-specific insulin resistance. 

A: after an injection of vehicle or Dex for 4 h, whole body insulin resistance was assessed using a euglycemic-hyperinsulinemic clamp. Insulin [HumulinR (3 mU·min⁻¹·kg⁻¹)] and d-glucose (50%) were continuously delivered (by a cannula inserted into the left jugular vein) for 3 h. At regular intervals, blood samples taken from the tail vein were analyzed for glucose using a glucometer. The glucose infusion rate (GIR) was adjusted accordingly to maintain euglycemia. CON, control.

B–E: to determine tissue-specific insulin resistance, the skeletal muscle (gastrocnemius and soleus muscles from the hind leg; B and C) and heart (D and E) from control (C) and 4-h Dex (D)-treated animals were evaluated for phospho-insulin receptor substrate-1 [P-IRS-1 (Tyr989); C and E] and phospho-Akt [P-Akt (Ser473); B and D] and total IRS-1 (T-IRS-1) and total Akt (T-Akt) before and after 15 min of injection of rapid acting insulin (I) into the tail vein (8 U HumulinR) using Western blot analysis. Results [in arbitrary units (AU)] are means ± SE of 3–5 rats/group. *Significantly different from control; †significantly different from all other groups; #significantly different from control animals given insulin (P < 0.05).
Animal Care and Use Committee (Protocol No. A07-0273). Adult male Wistar rats (260–300 g) were obtained from the University of British Columbia Animal Care Unit. The synthetic glucocorticoid hormone Dex (1 mg/kg) or an equivalent volume of ethanol was administered by intraperitoneal injection to nonfasted rats, and animals were euthanized at 4 h. In the human body, the daily secretion of cortisol is ∼6–8 mg/m² (in a 70-kg adult male, this translates to ∼0.2 mg/kg). In response to stress, cortisol release is increased up to 10-fold of the basal value (2 mg/kg) (13). For exogenous administration, dosing with corticosteroids depends on the disease condition and varies from 75 to 300 mg/day (∼1–4 mg/kg). Previous studies using an euglycemic-hyperinsulinemic clamp have determined that this dose of Dex induces whole body insulin resistance within 4 h (20, 43).

Euglycemic-hyperinsulinemic clamp. Whole animal insulin resistance was assessed using an euglycemic-hyperinsulinemic clamp, as previously described (43). This procedure involves the simultaneous intravenous infusion of insulin [HumulinR (3 mU·min⁻¹·kg⁻¹)], to inhibit endogenous hepatic production) and d-glucose (50%) for 3 h; the quantity of exogenous glucose required to maintain euglycemia is a reflection of the net sensitivity of target tissues (mainly skeletal muscle) to insulin. At regular intervals, a small amount of blood taken from the tail vein was analyzed for glucose (using a glucometer, AccuSoft Advantage). The glucose infusion rate was adjusted accordingly to maintain euglycemia.

Tissue-specific responses to insulin. To assess tissue-specific insulin resistance, the skeletal muscle (gastrocnemius and soleus muscles from the hind leg) and heart from control animals and 4-h Dex-treated animals were evaluated for total and phospho-insulin receptor substrate-1 (IRS-1) and Akt before and after 15 min of injection of rapid-acting insulin into the tail vein (8 units HumulinR) using Western blot analysis (18, 23). At this early time point, there was no significant reduction in blood glucose with insulin.

Myocardial glycogen content. Frozen cardiac tissue was powdered, weighed, incubated at 85°C (10 min) with 1 N NaOH, and followed by neutralization with 1 N HCl. The neutralized sample was subjected to further acid hydrolysis with 6 N HCl (85°C, 2 h) (32). After neutralization with 5 N NaOH, samples were subjected to glucose analysis using a glucokinase assay kit. The presence of cardiac glycogen was confirmed by visualization after periodic acid-Schiff staining (21). Where indicated, animals were administered mifepristone [RU-486 (20 mg/kg)] 1 h before Dex. After 4 h of Dex, hearts were isolated and frozen, and powdered tissue was used to measure cardiac glycogen. We have previously reported that phosphorylation of AMPK was inhibited by acute intralipid infusion (19). To determine the effect of AMPK inhibition on cardiac glycogen accumulation, animals were anesthetized with pentobarbital sodium, and the left jugular vein was cannulated. Intralipid (5%, 1.2 ml·kg⁻¹·h⁻¹) or vehicle (saline) was then infused over a period of 6 h, after which hearts were removed for the determination of glycogen. In some animals, Dex was administered 2 h after the intralipid infusion was initiated.

Subcellular compartmentalization of glucose transporter 4. Membrane fractions were isolated by a previously described method using a sucrose density gradient (14). With Western blot analysis, identification of glucose transporter 4 (GLUT4) protein was done using rabbit polyclonal GLUT4 as the primary antibody and mouse anti-rabbit horseradish peroxidase as the secondary antibody. Na⁺/K⁺-ATPase was used as a plasma membrane marker.

Immunoprecipitation and Western blot analysis. After Dex treatment, heart homogenates (500 µg protein) were immunoprecipitated using a rabbit monoclonal total Akt substrate of 160 kDa (AS160) antibody (3 h, 4°C). The immunocomplex was pulled down with protein A/G-Sepharose for 3 h, separated, boiled for 5 min at 95°C in Laemmli buffer, and subjected to SDS-PAGE. Western blot analysis using antibodies against AS160, phospho-(Ser/Thr) Akt substrate (PAS), phospho-Akt (Ser473, Thr308), total and phospho-AMPK-α (Thr172), and phospho-acetyl-CoA carboxylase (ACC; Ser79) was then performed as previously described (2). Measurement of the phosphorylated form of AMPK, ACC, GS, and GS kinase (GSK)-3β is a surrogate for the estimation of their activities. This was done using Western blot analysis. Reaction products were visualized using an ECL detection kit and quantified by densitometry.

Measurement of mRNA. mRNA levels were measured using quantitative real-time PCR. cDNA was synthesized from 1 µg RNA and purified using a sample purification kit (QiAGEN). RNA levels were determined from standard curves generated for each primer. The sample run was carried out for 40 cycles. The oligonucleotide primers were as follows: GLUT4 mRNA, forward 5′-GGGAAAAGAACAA- CAACAGT-3′ and reverse 5′-TGAGGAAAACAGAGAGTG-3′; AMPK-α₁ mRNA, forward 5′-GCAAGAGATCCAGAACCCTG-3′ and reverse 5′-CTCCTTTTCCTCAAACCTCTCC-3′; and AMPK-α₂ mRNA, forward 5′-GCTGTGATCGCAAAATTAT-3′ and reverse 5′-GCATCAGCAGATGGCAAATA-3′. Sample amplifications were done with the help of a fluorescent SYBR green dye (Roche Applied Science) in a Roche Applied Science Light Cycler system. β-Actin was used as an internal reference.
Glucose-6-phosphate content. Glucose-6-phosphate was determined in perchloric acid extracts of frozen ventricular tissue using standard spectrophotometric techniques (6, 26).

Glucose uptake in cardiomyocytes. Ventricular calcium-tolerant myocytes were prepared by a previously described procedure (41). Cells were plated on laminin-coated culture plates (60 mm, to a density of 300,000 cells/well). Glucose uptake was evaluated using radiolabeled 2-deoxyglucose (9). Briefly, myocytes were incubated in a glucose-free DMEM containing 0.2% fatty acid-free BSA and pyruvate (1.0 mM) as the energy source. Dex (100 nM) was then added to the incubation media for 20 min. A radioactive mixture (containing 5 μCi of [2-deoxy-3H]glucose) was added to the plates, and incubation was continued for another 10 min. After removal of the buffer, cardiomyocytes were washed with cold PBS (2×) and lysed using NaOH, and lysates were used to determine the radioactivity. 2-Deoxyglucose uptake was expressed as nanomoles per milligram per minute.

Materials. The ECL detection kit was purchased from Amersham Canada. Akt, phospho-Akt (Ser273/Thr308), AMPK, phospho-AMPKα, GS, phospho-GS, GSK-3-β, AS160, PAS, Na^+−K^+−ATPase, and GAPDH antibodies were obtained from Cell Signaling (Danvers, MA). GLUT4 antibody was purchased from Abcam (Cambridge, MA). All other chemicals were obtained from Sigma Chemical.

Statistical analysis. Values are means ± SE. Wherever appropriate, one-way ANOVA followed by Tukey or Bonferroni tests or the unpaired Student’s t-test was used to determine differences between group mean values. The level of statistical significance was set at P < 0.05.

RESULTS

Cardiac tissue has limited influence on whole body insulin resistance induced by Dex. We have previously reported that an injection of Dex for 4 h was not associated with either hyperinsulinemia or hyperglycemia (43). Nevertheless, using the euglycemic-hyperinsulinemic clamp, a direct measure of insulin sensitivity, Dex lowered the glucose infusion rate necessary to maintain euglycemia (Fig. 1A). We assessed the effects of Dex on the responses of skeletal muscle and cardiac tissue to insulin. In skeletal muscle, both basal and insulin-stimulated phosphorylation of IRS-1 (Fig. 1C) and Akt (Fig. 1B) were reduced after 4 h of Dex. These effects were not observed in cardiac tissue, which demonstrated a normal response to insulin when IRS-1 (Fig. 1E) and Akt (Fig. 1D) phosphorylation were measured. After 4 h of Dex, total IRS-1 and Akt did not change in skeletal and cardiac muscle compared with control (Fig. 1, B−D). Thus, after Dex, cardiac tissue has a limited contribution toward the development of whole body insulin resistance.

Buildup of cardiac glycogen after Dex is coupled to GLUT4 translocation. Even though Dex did not impede cardiac insulin signaling, we have previously reported a decline in cardiac glucose oxidation after Dex (43). In the presence of lower glucose oxidation, we hypothesized that glucose entering into the heart would be converted into glycogen. Indeed, Dex induced an approximately twofold increase in the cardiac glycogen content measured enzymatically (Fig. 2A) or by histochemical staining (Fig. 2B). This effect of Dex on glycogen was partially related to receptor activation because although RU-486 reduced the Dex-induced increase in cardiac glycogen, the levels observed were still higher than control (control: 37.8 ± 0.50 μg/g dry wt, Dex: 69.7 ± 1.5 μg/g dry wt, and Dex + RU-486: 44.6 ± 2.1 μg/g dry wt, P < 0.05). In addition to a reduction in glucose oxidation, it was unclear whether changes in glucose transport could also contribute

Fig. 3. Subcellular localization of glucose transporter 4 (GLUT4) protein. A and B: after Dex, heart homogenates were prepared and subjected to plasma membrane (PM; A) and intracellular membrane (IM; B) separation using a sucrose gradient. Identification of GLUT4 protein was carried out using rabbit polyclonal GLUT4 as the primary antibody and mouse anti-rabbit horseradish peroxidase as the secondary antibody. Na^+−K^+−ATPase was used as a PM marker. Quantitative real-time PCR enabled the determination of GLUT4 mRNA in hearts from control and Dex-treated animals. Results are means ± SE of 3−5 rats/group. *Significantly different from control (P < 0.05).
toward the accumulation of glycogen. Interestingly, Dex-treated hearts exhibited a higher glucose-6-phosphate content compared with control (control: 2.67 ± 0.16 μmol/g dry wt and Dex: 3.31 ± 0.20 μmol/g dry wt, P < 0.05). More importantly, after 4 h of Dex, measurement of GLUT4 at the plasma membrane revealed an excess presence of this transporter protein at this location (Fig. 3A). Usually, this observation is accompanied by a decrease in GLUT4 in the intracellular pool. However, in the present study, the Dex-induced increase in plasma membrane GLUT4 was also accompanied by an increase in GLUT4 in the intracellular membrane fraction (Fig. 3B). This latter effect was well correlated with increased GLUT4 mRNA (Fig. 3B, inset). Dex also increased glucose uptake directly in isolated cardiomyocytes (control: 4.2 ± 0.85 nmol·mg⁻¹·min⁻¹ and Dex: 9.86 ± 1.74 nmol·mg⁻¹·min⁻¹, P < 0.05).

Dex augments both total and phosphorylated cardiac AMPK. In addition to Akt signaling, cardiac GLUT4 translocation is also controlled by AMPK (45). In the presence of a normal Akt signal, we measured AMPK and found an increase in both total (Fig. 4C) and phospho-AMPK phosphorylation (Fig. 4A) after 4 h of Dex. This change in AMPK total protein was accompanied by a modest but insignificant increase in AMPK-α2 (Fig. 4E) but a significant increase in AMPK-α1 (Fig. 4D) gene expression. Once activated, AMPK phosphorylates and inactivates ACC, facilitating fatty acid oxidation. We measured ACC phosphorylation as a measure of AMPK activity. ACC phosphorylation was significantly increased in Dex-treated hearts compared with control hearts (Fig. 4B). To substantiate the role of AMPK in the Dex-induced accumulation of cardiac glycogen, intralipid was used to inhibit AMPK phosphorylation. Intralipid lowered the cardiac glycogen accumulation that was observed after Dex (control: 37.4 ± 1.8 μg/g dry wt, Dex: 66.2 ± 2.0 μg/g dry wt, and Dex + intralipid: 45.9 ± 0.7 μg/g dry wt, P < 0.05).

Phosphorylation of AS160 is mainly regulated by AMPK. AS160 regulates GLUT4 translocation to the plasma membrane by retaining this transporter in intracellular membranes, a function that is lost upon its phosphorylation (22). The major upstream regulators of AS160 phosphorylation include Akt and...
AMPK. Immunoprecipitation of AS160 followed by Western blot analysis demonstrated no change in Akt phosphorylation at Ser$^{473}$ and Thr$^{308}$ in Dex-treated hearts (Fig. 5, A and B). However, there was a significant increase in AMPK phosphorylation at Thr$^{172}$ (Fig. 5C), which correlated well with AS160 phosphorylation, as reflected by an increase in PAS (a measure of phosphorylation at Ser and Thr sites of AS160; Fig. 5D).

GS undergoes robust dephosphorylation with acute administration of Dex. In addition to the contributions by GLUT4-delivered glucose and the reduction of glucose oxidation toward glycogen synthesis after Dex, enzymatic control of this stored polysaccharide is also an important factor that controls its accumulation. GS, the rate-limiting enzyme for glycogen synthesis, is activated upon dephosphorylation (26). In Dex-treated hearts, there was a considerable reduction in the phos-

Fig. 5. AMPK regulation of Akt substrate of 160 kDa (AS160). Animals were treated with Dex, and, at 4 h, hearts from control and Dex-treated animals were isolated. To examine the association among AS160, Akt, and AMPK, AS160 was first immunoprecipitated using a total AS160 antibody. The immunocomplex was then immunoblotted with anti-P-Akt [Ser$^{473}$ (A) and Thr$^{308}$ (B)], anti-P-AMPK [Thr$^{172}$ (C)], phospho-(Ser/Thr) Akt substrate [PAS; Ser/Thr (D)], and anti-AS160 (inset). IP, immunoprecipitation. Results are means ± SE of 3–5 rats/group. *Significantly different from untreated control animals ($P < 0.05$).
phorylation of GS (Fig. 6, bottom). The major upstream kinase that regulates GS phosphorylation is GSK-3-β, whose activity, in turn, is reduced by its phosphorylation. As GSK-3-β phosphorylation was augmented (Fig. 6, top), our data suggest that cardiac glycogen accumulation after Dex is also dependent on the phosphorylation states of these two rate-limiting enzymes.

**DISCUSSION**

Chronically, increased levels of endogenous glucocorticoids are known to cause Cushing’s syndrome, a condition that is characterized by obesity, insulin resistance, increased lipid mobilization, and hypertension (28, 58). Exogenous delivery of glucocorticoids as anti-inflammatory and immunosuppressive agents is also associated with myocardial failure when administered chronically (35). We attempted to examine the acute effects of Dex specifically related to cardiac metabolism, given the injurious effects that excess triglyceride (30) and glycogen (1) have on the heart. We have previously reported an enlargement in the coronary lipoprotein lipase pool, with a subsequent increase in fatty acid delivery and augmented cardiac triglyceride accumulation (20, 42, 43). With carbohydrate metabolism, Dex promoted the expression of pyruvate dehydrogenase kinase 4, which is known to inhibit pyruvate dehydrogenase and pyruvate flux and, therefore, glucose oxidation (43). Under these circumstances, we proposed that glucose disposal occurred by its conversion to glycogen. In the present study, our data suggest that AMPK-mediated glucose entry combined with the activation of GS and the previously reported reduction in glucose oxidation (43) act together to promote glycogen storage.

With insulin resistance, metabolism in multiple organ systems, including the heart, is altered, which is believed to be an important factor in increased morbidity and mortality (5, 7). Measurement of insulin sensitivity using the euglycemic-hyperinsulinemic clamp revealed the presence of whole body insulin resistance with acute Dex treatment, suggesting that any change in cardiac metabolism that is exhibited by Dex may be a consequence of the prevalent reduction of insulin sensitivity. Nevertheless, we also determined the responses of skeletal muscle and cardiac tissue to insulin; unlike skeletal muscle, cardiac tissue responded normally to insulin. Under these conditions, it is possible that the effects of Dex on cardiac metabolism are also related to direct effects of this glucocorticoid on the heart. Glucocorticoids work through multiple mechanisms to bring about their desired effects. These include a specific cytosolic receptor-mediated event and specific and nonspecific membrane-bound receptor-mediated effects through which glucocorticoids bring about genomic and nongenomic outcomes (8, 10, 11). Given our recently reported observation that Dex activated AMPK (a metabolic switch that plays an important role in maintaining cellular energy homeostasis) phosphorylation in isolated cardiomyocytes within 60 min (20), and the use of RU-486 in our present study to reduce cardiac glycogen accumulation, our data suggest that the effects of Dex on cardiac metabolism in vivo may be linked to its direct impact on the heart. At present, the mechanism by which Dex increases the phosphorylation of AMPK is unknown and could include changes in the AMP-to-ATP ratio (17) or an activation of a Ca²⁺/calmodulin-dependent protein kinase kinase (49).

AMPK is known to inhibit anabolic and promote catabolic processes leading to the conservation of cellular ATP levels. It does so through multiple mechanisms including increased delivery and metabolism of both glucose and fatty acids (16,
In this context, and related to glycogen, AMPK is known to inhibit the formation of this storage form of glucose in skeletal muscle (40, 50, 56). In the heart, both low-flow ischemia (37) and exercise (34) increase AMPK activity, which is correlated to a reduction in glycogen content. Unexpectedly, our results suggest that the accumulation of glycogen with Dex was associated with increased phosphorylation of AMPK, a phenomenon that is observed in transgenic models of AMPK activation. In these models, mutation of regulatory γ-subunits (γ1 R70Q, γ2 N488I, and γ2 R531G) increased AMPK activation and facilitated glycogen accumulation (1, 12, 15, 27). It is possible that the intrinsic property of Dex to block glucose oxidation counteracts the ability of AMPK to prevent the storage of this carbohydrate. An additional explanation for this occurrence could be related to the effect of AMPK to decrease malonyl CoA, thereby removing its inhibition on carnitine palmitoyltransferase I and promoting fatty acid oxidation (42). The resultant blockade of glucose oxidation, as suggested by the Randle hypothesis, could explain the increase in glycogen storage (44). Whatever the mechanism, our data suggests that with carbohydrate metabolism, AMPK phosphorylation in the presence of Dex is associated with an anabolic function.

Under basal conditions, only a small percentage of GLUT4 resides at the plasma membrane, with the remaining fraction being redistributed in endosomal recycling and GLUT4 storage compartments (25, 46). Translocation of this transporter protein from the intracellular pool to the plasma membrane is regulated largely by the phosphatidylinositol 3-kinase-Akt pathway, in addition to AMPK. These kinases, by phosphorylating and inactivating AS160 (which has multiple phosphorylation motifs at Ser and Thr residues), removes the constraint that AS160 has on GLUT4, allowing the trafficking of this transporter to the membrane surface (22, 51, 52). Indeed, the increase in plasma membrane GLUT4 with Dex was well correlated to an increase in PAS, a measure of phosphorylation at Ser and Thr sites of AS160. To determine the contribution of Akt and AMPK toward this increased AS160 phosphorylation, we used immunoprecipitation to pull down the trimeric complex containing phospho-Akt, phospho-AMPK, and AS-160 and immunoblotted for the respective phosphoproteins. The present study suggests that after Dex, in the presence of normal insulin signaling, AMPK-mediated phosphorylation of AS160 is the predominant factor that controls cardiac GLUT4 movement.

Increased substrate availability plays an important role in glycogen synthesis. Thus, the increase in glucose uptake and glucose-6-phosphate after Dex could be an important contributing feature in glycogen accumulation. Other factors include alterations in glucose oxidation (43) and changes in the enzymes that control glycogen synthesis or breakdown. In skeletal muscle, glycogen regulation by GSK-3-β and GS is well established. AMPK is known to phosphorylate GS, making it prone to further phosphorylation by casein kinase-1 and GSK-3-β, leading to its inactivation (40, 50). The relationship among AMPK, GSK-3-β, and glycogen has yet to be resolved in the heart. For example, Mora et al. (33) showed that cardiac glycogen levels are regulated independently of insulin’s ability to phosphorylate GSK-3-β and stimulate GS. In the present study, phosphorylation of GS after Dex administration decreased, an effect closely associated with an increase in GSK-3-β phosphorylation. This effect of Dex on GS in the presence of increased AMPK phosphorylation was uncommon. As AMPK has been recently shown to activate GS through a GSK-3-β-dependent pathway in HepG2 cells (54), our data suggest that through multiple mechanisms, AMPK activation with Dex is associated with glycogen storage.

**Limitation of the study.** When examining the effects of AMPK inhibition on the heart, studies have used dominant negative AMPK overexpression or short interfering RNA to decrease AMPK activity. One limitation of this study is the use of intralipid to inhibit AMPK. This is because intralipid, in addition to its effects on AMPK, is also known to affect insulin signaling, and therefore glucose metabolism, by decreasing IRS (Tyr) and Akt (Ser) phosphorylation in the liver and skeletal muscle (4, 38). Thus, the decrease in cardiac glycogen after Dex + intralipid could be a result of both AMPK inhibition and reduced insulin signaling.

**Conclusions.** In summary, acute Dex administration was associated with a significant accumulation of myocardial glycogen. One way by which this process is made possible is through AMPK-mediated augmentation of glucose uptake, coupled to its regulation of GS, a key enzyme involved in glycogen synthesis (Fig. 7). Given the contribution of glycogen storage in eliciting cardiac hypertrophy, ventricular arrhythmias, and conduction system disorders, the results from the present study could help in limiting the deleterious effects of long-term excesses in endogenous or exogenous glucocorticoids on the heart.

![Fig. 7. Schematic mechanism of how Dex regulates cardiac glycogen through AMPK.](http://ajpheart.physiology.org/)
AMPK CONTROL OF CARDIAC GLYCOGEN

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GRANTS

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