Parallel Stimulation of Glucose and Mg\textsuperscript{2+} Accumulation by Insulin in Rat Hearts and Cardiac Ventricular Myocytes

Andrea M.P. Romani, Veronica D. Matthews, Antonio Scarpa

Abstract—The stimulation of β-adrenoceptors in cardiac cells results in a rapid loss of cellular Mg\textsuperscript{2+}. Because insulin physiologically counteracts several of the cellular effects mediated by the activation of β-adrenoceptors and the elevation of cytosolic cAMP levels, we investigated whether insulin administration could prevent Mg\textsuperscript{2+} mobilization from rat hearts and ventricular myocytes. Rat hearts were perfused in a retrograde Langendorff system, and the changes in extracellular Mg\textsuperscript{2+} were measured by atomic absorbance spectrophotometry. Pretreatment of the hearts with 6 μmol/L insulin completely prevented the Mg\textsuperscript{2+} extrusion induced by the β-adrenergic agonist isoproterenol. Furthermore, the administration of insulin per se induced an accumulation of Mg\textsuperscript{2+} by the heart. This accumulation was small but detectable in the presence of 25 to 35 μmol/L [Mg\textsuperscript{2+}]\textsubscript{i}, and increased in proportion to [Mg\textsuperscript{2+}]\textsubscript{o}. Insulin-mediated Mg\textsuperscript{2+} accumulation was not observed in hearts perfused with a medium devoid of glucose or with a medium containing the inhibitors of glucose transport, cytochalasin B and phloretin. Insulin-stimulated [\textsuperscript{3}H]2-deoxyglucose accumulation was measured in collagenase-dispersed cardiac ventricular myocytes in the presence of varying levels of [Mg\textsuperscript{2+}]\textsubscript{o}. Glucose transport was not observed below 25 μmol/L [Mg\textsuperscript{2+}]\textsubscript{o}, and it also increased in proportion to [Mg\textsuperscript{2+}]\textsubscript{o}. Taken together, these results indicate the presence of a major uptake of Mg\textsuperscript{2+} into cardiac cells that is stimulated by insulin and may require the insulin-induced operation of a glucose transporter. Hence, extracellular and/or intracellular Mg\textsuperscript{2+} may modulate glucose transport and/or utilization. (Circ Res. 2000;86:326-333.)

Key Words: Mg\textsuperscript{2+} ■ cardiac myocytes ■ hearts ■ insulin ■ glucose transport

In recent years, a large number of reports have indicated that the selective stimulation of β-adrenoceptors results in a marked extrusion of cellular Mg\textsuperscript{2+} from cardiac myocytes, hepatocytes, and other cell types into the extracellular compartment. In addition, the infusion of isoproterenol or catecholamine results in a 15% to 20% increase in the total serum Mg\textsuperscript{2+} content. At the cellular level, Mg\textsuperscript{2+} extrusion can be elicited by the administration of forskolin or cell-permeant cAMP analogues (eg, 8-bromo-cAMP) and be inhibited by the administration of Rp-cAMP, a cell-permeant blocking agent specific for protein kinase A. Taken together, these results support the idea that Mg\textsuperscript{2+} extrusion is mediated via a cAMP-dependent process, most likely the phosphorylation of a specific Mg\textsuperscript{2+} transporter.

Experimental evidence suggests a role for insulin in regulating cellular or tissue Mg\textsuperscript{2+} content. Our laboratory has recently reported that because of its ability to prevent cAMP production and accelerate cAMP catabolism via phosphodiesterase, insulin can effectively modulate the extrusion of Mg\textsuperscript{2+} induced by β-adrenergic agonists in liver cells. In addition, evidence has been provided indicating that insulin increases cytosolic free [Mg\textsuperscript{2+}] in beta pancreatic islets, 3T3 fibroblasts, and platelets by promoting an entry of Mg\textsuperscript{2+} across the plasma membrane and/or a release of Mg\textsuperscript{2+} from an intracellular organelle(s). Last, a marked decrease in cellular Mg\textsuperscript{2+} content has been observed in diabetes types I and II and both in humans and animals, and this decrease has been suggested to be a possible cause of the long-term complications associated with diabetes.

In the present study, the ability of insulin to modulate cellular Mg\textsuperscript{2+} in cardiac myocytes was investigated. The results obtained indicate that insulin can modulate cellular Mg\textsuperscript{2+} content by limiting the amount of Mg\textsuperscript{2+} extruded from cardiac cells stimulated by β-adrenergic agonists or by inducing a Mg\textsuperscript{2+} accumulation in the cells. Furthermore, the presence of a synergism between glucose transport and Mg\textsuperscript{2+} accumulation in cardiac cells suggests a key role of Mg\textsuperscript{2+} in controlling glucose utilization for energetic purposes within the cell.

Materials and Methods

Chemicals
Collagenase (CLS-1) was from Worthington. [\textsuperscript{3}H]2-Deoxyglucose was from Amersham. All other chemicals were from Sigma Chemical Co. Whatman glass fiber filters were from Fisher.
Rat Heart Perfusion
Male Sprague-Dawley rats (250 g body weight) were anesthetized by intraperitoneal injection of sodium pentobarbital. The heart was removed and perfused in a Langendorff system at a flow rate of 7 mL/min with a medium containing (mmol/L) NaCl 120, KCl 3, KH₂PO₄ 1.2, CaCl₂ 1.2, MgCl₂ 1.2, glucose 20, HEPES 10, and NaHCO₃ 12, pH 7.2, equilibrated at 37°C with O₂/CO₂ (95:5 [vol/vol]). The [Mg⁺²], in the perfusion medium was varied from 0 to 1000 μmol/L. Where indicated in the figures, isoproterenol, 8-chloro-cAMP, or insulin was added to the perfusion medium.

In the experiments performed in the absence of extracellular glucose, 5 mmol/L pyruvate and 5 mmol/L lactate were added to the perfusion medium. Alternatively, pyruvate and lactate were added to the perfusion medium in addition to glucose. Cytochalasin B or phloretin was dissolved in the perfusion medium 5 minutes before the perfusion medium. Alternatively, pyruvate and lactate were added to the perfusion medium. Cytochalasin B or phloretin was dissolved in the perfusion medium 5 minutes before the perfusion medium. Alternatively, pyruvate and lactate were added to the perfusion medium.

Isolation of Cardiac Ventricular Myocytes and Determination of Mg²⁺ Accumulation
Cardiac ventricular myocytes were isolated by collagenase digestion as described by De Young et al. An aliquot of cell suspension was washed at 600 g for 1 minute and transferred into the incubation medium described previously, in the presence of varying concentrations of extracellular Mg²⁺ or glucose. Mg²⁺ accumulation into the cells was determined as reported previously.

Determination of Glucose Transport
For the experiments in perfused hearts, 0.2 mCi/mL [H]2-deoxyglucose was added to the perfusion medium. Half-milliliter aliquots of the perfusate were collected in duplicate and transferred in scintillation vials to measure the radioactivity by β-scintillation counting in a Beckman LS7000 counter. At the end of the perfusion, the heart was homogenized in 10% HNO₃ and extracted overnight. The Mg²⁺ content in the acid supernatant was measured by atomic absorbance spectrophotometry as described previously.

Statistical Analysis
The data were reported as mean±SE. Data were first analyzed by 1-way ANOVA. Multiple means were then compared by the Tukey multiple comparison test, which was performed with a q value established for significance at P<0.05.

An expanded Materials and Methods section is available online at http://www.circresaha.org.

Results
The administration of 1 or 10 μmol/L isoproterenol to rat hearts perfused in a Langendorff system resulted in a detectable increase in heart contractility (not shown) and in a marked extrusion of Mg²⁺ from the organ into the perfusate (Figure 1A). Mg²⁺ efflux became evident within 2 minutes after the addition of the β-adrenergic agonist to the perfusion medium and persisted for an additional 5 minutes before returning toward basal levels. The time course of these changes was independent of the dose and persistence of the agonist in the perfusion medium, the rate of contractility elicited by the adrenergic agonist, and [Mg²⁺], as already reported. Isoproterenol-induced Mg²⁺ efflux from rat hearts perfused in a Langendorff retrograde manner was induced by administration of 1 or 10 μmol/L isoproterenol. Insulin (10 mU/mL=6 nmol/L) was administered 5 minutes before 10 μmol/L isoproterenol. Data were determined every 30 seconds but are represented at 90-second intervals for clarity. Data are mean±SE of 5 different hearts for all experimental conditions. *P<0.05 vs control.

Figure 1. Efflux of Mg²⁺ from perfused rat hearts stimulated by isoproterenol (iso or isoprot.) in the absence (A) or presence (B) of insulin. Mg²⁺ efflux from rat hearts perfused in a Langendorff retrograde manner was induced by administration of 1 or 10 μmol/L isoproterenol. Data were determined every 30 seconds but are represented at 90-second intervals for clarity. Data are mean±SE of 5 different hearts for all experimental conditions. *P<0.05 vs control.

Hence, the possibility that insulin induced Mg²⁺ accumulation into cardiac cells was further investigated by increasing [Mg²⁺], in the perfusate from the contaminant concentration present in Figure 1. Insulin administration resulted in a small but detectable Mg²⁺ accumulation when the heart was perfused with 25 μmol/L Mg²⁺, (not shown). The decrease in
Mg\textsuperscript{2+} content in the perfusion medium, an indication of Mg\textsuperscript{2+} accumulation into cardiac cells, increased progressively in hearts perfused with 35 or 50 \(\mu\)mol/L [Mg\textsuperscript{2+}], (Figure 3A) or higher levels of [Mg\textsuperscript{2+}], (not shown). In Figure 3B, the net Mg\textsuperscript{2+} accumulation by the perfused heart during 8 minutes of insulin administration is reported as the total amount of Mg\textsuperscript{2+} disappearing from the perfusate. The net Mg\textsuperscript{2+} accumulation was accounted for by \(\approx 500\) to 600 nmol/g heart for [Mg\textsuperscript{2+}], of 100 and 200 \(\mu\)mol/L and \(\approx 700\) to 800 nmol/g heart for [Mg\textsuperscript{2+}], of 500 or 1000 \(\mu\)mol/L. The Mg\textsuperscript{2+} determination in acid extracts of the heart at the end of the experiment indicates an increase in total tissue Mg\textsuperscript{2+} content from 61.97\(\pm\)3.24 to 71.42\(\pm\)3.18 and to 77.21\(\pm\)4.50 nmol/mg protein\textsuperscript{-1} in hearts perfused with 200 and 1000 \(\mu\)mol/L [Mg\textsuperscript{2+}], respectively (\(P<0.05\), n=4 for all experimental conditions).

A similar inhibitory effect of insulin on isoproterenol- or cAMP-induced Mg\textsuperscript{2+} extrusion has been observed in perfused liver.\textsuperscript{6} However, insulin per se did not induce any detectable Mg\textsuperscript{2+} uptake into liver cells, regardless of the [Mg\textsuperscript{2+}], used.\textsuperscript{6} One notable difference between cardiac and liver cell metabolism is the different class of glucose transporter present in the plasma membrane, namely, Glut1 and Glut4 in cardiac cells\textsuperscript{25} and Glut 2 in hepatocytes.\textsuperscript{25} Glut4 transporters (and Glut1 to a lesser extent),\textsuperscript{26} but not Glut2,\textsuperscript{25} are recruited to the sarcolemma by insulin administration. Therefore, we next investigated the possibility that glucose transport is involved in mediating the accumulation of Mg\textsuperscript{2+} induced by insulin.

The requirement of glucose transport for Mg\textsuperscript{2+} accumulation is supported by the data reported in Figure 4. In the presence of 50 \(\mu\)mol/L [Mg\textsuperscript{2+}], the absence of glucose in the perfusate (replaced with lactate and pyruvate, Figure 4B) completely prevented the insulin-mediated Mg\textsuperscript{2+} accumulation (Figure 4A). To exclude the possibility that the lack of Mg\textsuperscript{2+} accumulation observed under these experimental conditions could be attributable to the sudden change in metabolic substrate, in a separate set of experiments, 5 \(\mu\)mol/L pyruvate and 5 \(\mu\)mol/L lactate were introduced into the perfusion medium at the start, in addition to glucose. Glucose was removed at the time of insulin administration, to be reintroduced after hormone removal, but pyruvate and lactate were maintained throughout the experimental protocol. Also, under these experimental conditions, insulin administration did not result in an accumulation of Mg\textsuperscript{2+} in the heart (total tissue Mg\textsuperscript{2+} content was 64.0\(\pm\)6.4 versus 61.7\(\pm\)5.4 nmol...
Mg\(^{2+}\)/mg protein in control hearts versus insulin-treated hearts, \(n=4\) for both experimental conditions, \(P>0.05\). By contrast, when glucose was maintained throughout the experimental protocol in addition to pyruvate and lactate, the administration of insulin resulted in a disappearance of Mg\(^{2+}\) from the perfusate (Figure 4C) and an accumulation in the heart (total tissue Mg\(^{2+}\) content was 70.8\(\pm\)6.2.5 versus 60.8\(\pm\)3.4 nmol Mg\(^{2+}\)/mg protein \(\pm\) in the presence or in the absence of insulin, respectively).

In a separate set of experiments, cytochalasin B and phloretin were used as glucose transport inhibitors. Whereas cytochalasin B blocks the translocation of glucose transporters to the plasma membrane by disrupting cytoskeleton integrity, phloretin inhibits glucose transport operation at the plasma membrane by interacting at the extracellular site of the transporter.\(^{23,25}\) When 1\(\mu\)mol/L cytochalasin B or 10\(\mu\)mol/L phloretin was added to the perfusate in the presence of glucose, the insulin-induced Mg\(^{2+}\) accumulation in the heart was almost completely inhibited (Figure 5). Finally, when insulin-induced Mg\(^{2+}\) accumulation was measured at varying extracellular glucose concentrations, a minimal glucose concentration of 2 mmol/L appeared to be required for the Mg\(^{2+}\) accumulation to occur (Figure 6). Net Mg\(^{2+}\) accumulation accounted for 1.53\(\pm\)0.35 (n=4), 2.92\(\pm\)0.98 (n=4), and 17.80\(\pm\)2.32 nmol Mg\(^{2+}\)/mg protein \(\pm\) for insulin-stimulated hearts perfused in the presence of 2, 5, and 10 mmol/L glucose, respectively. The last 3 time points under the curve of uptake with 10 mmol/L glucose are significantly different \((P<0.05)\) compared with the corresponding time points reported in Figure 4A. Presently, we have no explanation for this discrepancy.

The presence of a synergism between glucose and Mg\(^{2+}\) accumulation is further corroborated by the results reported in Figure 7. Because nonphosphorylated glucose can cross the sarcolemma in either direction, \[^{1}H\]2-deoxyglucose, which remains trapped in the cytosol after the phosphorylation by hexokinase,\(^{25}\) was used to quantify the amount of glucose accumulated by cardiac ventricular myocytes after 5 minutes of stimulation by 10 \(\mu\)U/mL (6 nmol/L) insulin. Cardiac ventricular myocytes rather than perfused hearts were used to...
exclude possible artifacts related to perfusion flow rate and to cell heterogeneity. The data, reported in Figure 7A, indicate that $[\text{Mg}^2+]_o$ is required to observe an accumulation of glucose into cardiac cells. This accumulation accounted for 0.47±0.06 nmol glucose/10^6 cells at 50 μmol/L $[\text{Mg}^2+]_o$ and increased to 1.07±0.05, 1.68±0.06, and 2.56±0.05 nmol/10^6 cells when $[\text{Mg}^2+]_o$ was 100, 500, and 800 μmol/L, respectively. Under these experimental conditions, $\text{Mg}^2+$ accumulation was 26.9±6.1 nmol/10^6 cells for 5 minutes at 100 μmol/L $[\text{Mg}^2+]_o$ and 58.0±12.3 nmol/10^6 cells for 5 minutes at 500 μmol/L $[\text{Mg}^2+]_o$. (Figure 7B). Based on the total cellular $\text{Mg}^{2+}$ content of cardiac ventricular myocytes, these values account for increases of 10% and 22% in total $\text{Mg}^{2+}$ content, respectively.

After it had been determined that the presence of extracellular glucose or the operation of glucose transporter is necessary to observe insulin-induced $\text{Mg}^{2+}$ accumulation, rat hearts were perfused in the presence of pyruvate and lactate but in the absence of extracellular glucose, and stimulated by 10 μmol/L isoproterenol and 10 mU/mL insulin to determine whether the effect of insulin on the $\beta$-adrenoceptor-mediated $\text{Mg}^{2+}$ extrusion observed in Figures 1 and 2 could be ascribed to an inhibitory effect on $\beta$-adrenergic signaling and/or to a stimulated accumulation of $\text{Mg}^{2+}$ into the heart. As Figure 8A shows, in the presence of 50 μmol/L $[\text{Mg}^{2+}]_i$, but in the absence of extracellular glucose, insulin was still able to block the extrusion of $\text{Mg}^{2+}$ elicited by isoproterenol infusion. By contrast, in the presence of glucose, the administration of insulin before adrenergic agonist infusion resulted in an accumulation of $\text{Mg}^{2+}$ that could not be reverted by the subsequent infusion of isoproterenol (Figure 8B).

**Discussion**

The administration of $\beta$-adrenergic agonists to cardiac cells elicits a marked extrusion of cellular $\text{Mg}^{2+}$ in the extracellular compartment via an increase in cAMP and the activation of a specific Na$^+-\text{Mg}^{2+}$ exchanger. Recently, we have reported that insulin can modulate $\text{Mg}^{2+}$ content in liver cells by preventing the $\beta$-adrenoceptor–mediated $\text{Mg}^{2+}$ mobilization from the cell. The present study, undertaken to investigate whether insulin has a similar modulatory role in cardiac cells, provides several novel observations. First, it provides evidence for a role of insulin in preserving $\text{Mg}^{2+}$ content in cardiac cells by preventing the $\text{Mg}^{2+}$ mobilization induced by $\beta$-adrenergceptor stimulation. Second, it indicates that insulin induces an accumulation of $\text{Mg}^{2+}$ into cardiac cells through a transport mechanism that is linked to the operation of glucose transporter in the cardiac sarcolemma. Third and most important, it suggests that $\text{Mg}^{2+}$ is indispensable for the accumulation of...
accumulation is prevented (ie, absence of extracellular glucose; Figure 8A). This may suggest that insulin and β-adrenergic agonists regulate cellular Mg$^{2+}$ homeostasis by activating distinct Mg$^{2+}$ transport mechanisms and that insulin can inhibit the Mg$^{2+}$ extrusion mechanism as well as activate the Mg$^{2+}$ entry pathway. Because of the novelty of this observation, the physiological conditions that determine the modality of insulin action on cardiac Mg$^{2+}$ homeostasis require further investigation.

Because insulin does not stimulate Mg$^{2+}$ accumulation in the perfused liver regardless of [Mg$^{2+}$], in the perfusion medium, cardiac but not liver cells must possess a specific entry mechanism activated by insulin. One of the main differences between cardiac and liver cells is the different class of glucose transporter present in the plasma membrane of these 2 cell types. In cardiac myocytes, insulin induces glucose accumulation by recruiting Glut4 (10- to 20-fold increase) and Glut1 transporters (2-fold increase) from a preconstituted intracellular pool to the sarcolemma. The consequence of this recruitment is that glucose accumulation into cardiac myocytes increases severalfold and in a manner that is not simply proportional to the number of new transporters expressed in the sarcolemma. By contrast, liver cells possess a distinct glucose transporter (Glut2) that is not affected in number and operation by insulin.

### Involvement of Glucose Transport in Insulin-Mediated Mg$^{2+}$ Accumulation

The results obtained in the absence of external glucose or in the presence of the inhibitors of glucose transport, cytochalasin B and phloretin, are consistent with the idea that insulin-induced Mg$^{2+}$ accumulation requires operation and/or internalization of glucose transporters. Because insulin administration increases the expression of Glut4 to a great degree and Glut1 only marginally in the sarcolemma, it is conceivable that Glut4 is the main class of glucose transporters involved in Mg$^{2+}$ accumulation. Support for this hypothesis is provided by the effect of glucose transport inhibitors. Whereas phloretin blocks both Glut1 and Glut4 in the sarcolemma by interacting at the extracellular site of the transporter, cytochalasin B (by disrupting cytoskeletal integrity) mainly affects Glut4, by preventing the recruitment of this transporter to the sarcolemma after insulin administration. In addition, Mg$^{2+}$ accumulation requires a minimal extracellular glucose concentration of 2 mmol/L to occur, which falls well within the $K_m$ of the Glut4 transporter. However, because Mg$^{2+}$ accumulation increases proportionally with the extracellular glucose concentration, the additional involvement of the Glut1 transporter (with a higher $K_m$) cannot be altogether excluded. Last, it is interesting to note that insulin and isoproterenol stimulate an accumulation and an extrusion of Mg$^{2+}$, respectively, whereas they both induce a glucose accumulation in cardiac cells. Because insulin primarily activates Glut4 and isoproterenol activates Glut 1,$^{25}$ further indirect evidence is provided for the role of Glut4 in Mg$^{2+}$ accumulation.

Our data do not clearly indicate whether Mg$^{2+}$ is cotransported with glucose or whether the cation enters the cell through a transport pathway distinct from the glucose trans-

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**Figure 8.** Inhibitory effect of insulin (Insu) on isoproterenol (Iso)-induced Mg$^{2+}$ extrusion in the absence (A) or presence (B) of extracellular glucose. Mg$^{2+}$ efflux from rat hearts perfused in a Langendorff retrograde manner was elicited by administration of 10 μmol/L Iso. Insu (10 μU/mL = 6 nmol/L) was administered 3 minutes before Iso infusion. Perfusion medium contained 50 μmol/L [Mg$^{2+}$], 5 mmol/L lactate, 5 mmol/L pyruvate, and 15 mmol/L glucose. In panel A, glucose was removed from the incubation medium during Insu and Iso infusion. In panel B, extracellular glucose was maintained throughout the experimental protocol. Data were determined every 30 seconds but are represented at 90-second intervals for clarity. Data are mean ± SE of 4 different hearts for all the experimental conditions. Values of $P$ are as follows for panels A and B: A, $P<0.05$ vs control and insulin-treated hearts. B, $P<0.05$ vs control.

**Effect of Insulin on Cellular Mg$^{2+}$ Homeostasis**

The administration of insulin before isoproterenol (Figure 1) or cAMP addition (not shown) or after β-agonist administration (Figure 2) can completely prevent the extrusion of Mg$^{2+}$ elicited via activation of the β-adrenergic signaling pathway. These effects of insulin can be explained by the ability of insulin to desensitize β-adrenoceptors and to stimulate calmodulin-dependent phosphodiesterase, thereby limiting the production and inducing a more rapid degradation of cellular cAMP. Overall, these results are consistent with the inhibitory effect observed previously in the perfused liver and would indicate a more general and rapid degradation of cellular cAMP. Overall, these results are consistent with the inhibitory effect observed previously in the perfused liver and would indicate a more general and rapid degradation of cellular cAMP. Overall, these results are consistent with the inhibitory effect observed previously in the perfused liver and would indicate a more general and rapid degradation of cellular cAMP.
porters. However, the inhibitory effect of cytochalasin B or phloretin suggests that the Mg\(^{2+}\) entry mechanism is activated by insulin indirectly via glucose transporter operation. Moreover, it appears that glucose reintroduction can induce Mg\(^{2+}\) accumulation even after insulin is removed from the system (Figure 4A). Most likely, this phenomenon is due to the persistence of an activated Glut4 transporter in the sarcolemma that is able to transport glucose after its reintroduction. In view of the fact that a glucose-triggered Mg\(^{2+}\) accumulation has been observed in pancreatic beta cells,\(^{31}\) the possibility that Mg\(^{2+}\) accumulation is generally associated with glucose transporter operation is a suggestive hypothesis that requires further investigation. Mg\(^{2+}\) uptake in cardiac myocytes appears to be 1 order of magnitude larger than glucose accumulation. Based on an estimated cell volume (Reference 1 and references therein), the amount of Mg\(^{2+}\) accumulation can be calculated on the basis of the number of mitochondrial dehydrogenases support the hypothesis that Mg\(^{2+}\) accumulated into the cell may be rapidly redistributed from the cytosol into the mitochondria or other organelles and regulate rates of respiration or concentrations of substrates necessary for specific metabolic pathways.

Together with previous evidence in the literature, the data reported in the present study indicate a close link between glucose transport and Mg\(^{2+}\) accumulation in cardiac ventricular myocytes. Although this link may be present in other cell types, it may be predominant in the heart, in which insulin modulates the operation of glucose transporters. Furthermore, indirect support for this link is provided by the observation that cellular Mg\(^{2+}\) levels and glucose utilization are markedly reduced in diabetic humans and animals. The relevance of this relation under both physiological and pathological conditions remains to be elucidated.

Acknowledgments

This study was supported by National Institutes of Health grants HL-18708 and R9- AA-11593A1 and by the Diabetes Association of Greater Cleveland (grant No. 397-A-97).

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doi: 10.1161/01.RES.86.3.326

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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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