Correlation Between Decreased Myocardial Glucose Phosphorylation and the DNA Mutation Size in Myotonic Dystrophy

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Background Myotonic dystrophy, the most common form of adult muscular dystrophy, has been shown to be caused by amplification of CTG triplet repeat in the 3′ untranslated region of a protein kinase gene located on chromosome 19. Impaired glucose metabolism has been suggested as a possible explanation of brain and skeletal muscle involvement in this multisystem disease. We investigated whether myocardial glucose metabolism is impaired in myotonic dystrophy and whether this impairment is related to the size of the mutation.

Methods and Results The myocardial metabolic rate for glucose (MMRGlu, μmol·min⁻¹·g⁻¹), K1 (blood-to-tissue transfer constant), k2 (tissue-to-blood transfer constant), and k3 (phosphorylation rate constant) were determined in 17 control subjects and 12 patients with myotonic dystrophy by using parametric images generated from dynamic cardiac positron emission tomography (PET) and 18F-fluoro-2-deoxyglucose studies. The expansion of the CTG triplet repeats was analyzed in patients with the probe cDNA25 after EcoR1 digestion. Nonparametric tests were used to compare quantitative variables between control subjects and patients. The correlations between the size of the mutation and PET parameters were studied by linear regression. MMRGlu and k3 were significantly decreased in patients compared with control subjects (0.39±0.20 versus 0.64±0.25, P=.03, and 0.09±0.07 versus 0.24±0.21, P=.03, respectively), whereas K1 and k2 were not statistically different between control subjects and patients. MMRGlu and k3 correlate inversely with the length of the CTG triplet repeat (r=-.65 and P=.03 for MMRGlu, and r=-.85 and P=.001 for k3, respectively).

Conclusions In myotonic dystrophy, the observed reductions in MMRGlu and phosphorylation are inversely linked to the length of the mutation. This observation suggests that impaired modulation of a protein kinase involved in myocardial hexokinase activation may give a pathophysiological schema to relate the molecular defect and the abnormal myocardial metabolism in myotonic dystrophy. (Circulation. 1994;90:2629-2634.)

Key Words • myotonic dystrophy • tomography, positron emission • molecular biology • myocardial glucose metabolism

Myotonic dystrophy (DM) is the most common form of adult muscular dystrophy and is inherited in an autosomal dominant fashion. The disorder has recently been shown to be caused by an increased number of CTG trinucleotide repeats in the 3′ untranslated region of a protein kinase gene located on the q13.3 band of chromosome 19. The normal copy number of 5-35 repeats is exceeded in patients with DM, with the size of the expansion broadly correlating with the severity of the symptoms. In this multisystem disease, heart-related death has been estimated to be ~30%, involving mainly impairment of the conduction pathways consisting of sinus bradyarrhythmia, atrioventricular block and bundle-branch block, and ventricular arrhythmias. Left ventricular dysfunction appears to be rare and usually remains subclinical.

However, isotopic studies provided evidence of decreased left ventricular ejection fraction and abnormal wall motion during exercise in patients with DM, without macroscopic ischemic disease and with normal rest ventricular function. This observation suggests that there is a failure of the heart in DM to adequately adapt to stress that might progressively lead to resting myocardial dysfunction. Histological findings of the heart include fibrosis and fatty infiltration of conducting tissue as well as patchy myocardial involvement with myofibrillar degeneration and prominent l-bands at ultrastructural analysis. Although these histological features reflect clinical abnormalities, they do not provide a clue to the pathogenesis of heart involvement.

In vitro studies of skeletal muscles and in vivo studies of the brain demonstrated decreased glucose transport across cell's membrane. While free fatty acids served as the main energetic metabolites for the resting heart, glucose becomes a major fuel (other than lactate) for the heart under stress conditions. An appropriate supply of energy-giving substrates protects against the development of ischemic myocardial damage, abnormal propagation of currents that generate signals in excitable membranes, and impairment of ventricular contractile activity. Therefore, abnormal myocardial glucose utilization may contribute
to the failure of heart to appropriately adapt to stress and onset of myocardial dysfunction.

The aim of the present study was to study myocardial glucose utilization in adults with DM and without clinical myocardial involvement under the condition of enhanced myocardial glucose consumption.

**Methods**

The study protocol was approved by our institutional ethics committee. All subjects gave informed consent.

**Study Population**

**Patients**

Twelve patients with DM took part in the study. All of them completed the established clinical and electromyographic criteria for definite DM. All patients were ambulatory, and none had a past history of ischemic heart disease. The patients with DM, who were incapable of exercising on a treadmill or bicycle, underwent intravenous diprydomale 201Tl imaging and resting 99mTc radionuclide angiography to assess myocardial perfusion and left ventricular ejection fraction, respectively. When there were defects at 201Tl imaging, the patients underwent coronary angiography. The patients with DM were enrolled in the study if they had a normal 201Tl scan and/or coronary angiogram and if they had left ventricular ejection fraction of >45%.

**Control Subjects**

Seven age- and sex-matched subjects volunteered; none had a past history of coronary artery disease, and all had normal clinical, ECG, and echocardiography examinations.

**Positron Emission Tomography Imaging**

Before the study, an indwelling catheter was inserted in a forearm vein, allowing intravenous injection of tracers and blood sample withdrawal for biological measurements.

**Data Acquisition**

Subjects were positioned in the TTV03 time-of-flight positron emission tomography (PET) scanner (LETI, CEA). This instrument allows acquisition of seven cross-sectional images, 12 mm apart, with 7-mm in-plane resolution on a reconstructed image using a modified Hanning window function. The axial resolution is 9 mm for a direct plane and 7 mm for a cross plane. Transmission scans were obtained with a retractable 68Ge ring source and used for subsequent attenuation correction of the emission scans. To check positioning of the heart in the center of the field of view, we recorded a 5-minute rectilinear transmission scan before the examination. Correct positioning was maintained throughout the study by the use of laser beams and skin marks placed on the subject’s torso.

In myocardial blood flow (MBF) experiments, subjects and patients received an intravenous bolus injection of H215O (0.30 mCi/kg). Data were acquired in list mode during the 5 minutes after the occurrence of blood radioactivity in the left ventricular cavity. A dynamic series of images (15×4 seconds, 18×10 seconds) was reconstructed using a backprojection algorithm and a 0.5 mm−1 cutoff frequency-modified Hanning filter. Images were corrected for attenuation, random events, dead time losses, and scattered radiations as described elsewhere. The dead time losses were <10% for all studies. After completion of the MBF experiments, patients underwent a 18F-fluoro-2-deoxyglucose (FDG) PET study. Patients were administered a 50-g glucose PO load 60 minutes before FDG imaging. After the intravenous injection of 0.1 mCi/kg FDG, data were acquired in list mode over 60 minutes. A 20-minute static image recorded 40 minutes after injection was used to define myocardial regions of interest. This image was reconstructed using the same reconstruction procedure as described for the H215O study.

**Dynamic Reconstruction for FDG**

Regions of interest encompassing the anterior, septal, and lateral myocardial walls were drawn manually on three consecutive slices of the FDG image. Another region of interest was drawn in the left ventricular cavity (LVC) of the FDG PET slice, allowing the best visualization. H215O time-activity curves were generated in each myocardial region of interest. With the LVC time-activity curve as an input function, with a single tissue compartment and three parameters (K1, k2, and a spillover fraction fL) was fit to the PET data by minimizing a weighted least-squares criterion. We estimated MBF to be the blood-to-tissue transfer rate constant K1. The Marquardt-type optimizer was always provided with the same parameter initial values: K1 = 1.0 mL·min−1·mL−1, k2 = 0.01·min−1, and fL = 0.20.

FDG time-activity curves were generated in each myocardial region of interest, the sum of which was the global myocardial activity. Myocardial metabolic rate of glucose (MMRGLu, [μmol·min−1·g−1]) was calculated from a three-compartment model for FDG as previously described. The latter consists of FDG in plasma, FDG in tissue, and FDG-6-phosphate in tissue. The first-order rate constants, K1 and k2, refer to forward and reverse transport of FDG across the capillary and sarcolemmal membranes, respectively, whereas k3 refers to phosphorylation of FDG. MMRGLu can be estimated from the following equation:

\[
\text{MMRGLu} = \left(\frac{C_p}{LC}\right)(K1k3/k2+k3)
\]

In this expression, Cp is plasma glucose concentration, and LC is the lumped constant (1.49 in our study). The FDG model was fit to the global myocardial kinetic data to determine the rate constants K1, k2, and k3.

The ECG was monitored continuously during the examination as well as 30 minutes before and 60 minutes after the PET scan. Blood pressure was measured before injection and every 2 minutes during the examination. The pressure product (heart rate x systolic blood pressure) was defined before glucose loading and during PET studies.

Before (H0) and 60 minutes after glucose loading (H1, just before the FDG injection) and 45 minutes after the FDG injection (H2), blood samples were drawn for measurement of glycemia (G; mmol/L), insulinemia (UI/L), free fatty acids (mmol/L), lactate (mmol/L), and pyruvate (mmol/L).

All subjects underwent a two-dimensional echocardiographic examination to measure septal and posterior wall thicknesses and systolic and diastolic left ventricular diameters.

**CTG Trinucleotide Expansion Status in DM Patients**

DNA was extracted from peripheral blood samples as previously reported. DNA (10 μg) was digested with EcoRI following the manufacturer’s conditions and electrophoresed on agarose gel (0.8%) for 48 hours. The DNA fragments were transferred to Hybond N membrane (Amersham). Filter was hybridized to the (a-32P)-dCTP-labeled CDNA25 probe (3) at 65°C for 18 hours. Before autoradiography, the filter was washed to a final stringency of 0.1× SSC, 0.1% SDS at 65°C for 10 to 30 minutes.

**Statistical Analysis**

All parameters were expressed as mean±SD values. Parameters were compared between control subjects and patients using nonparametric tests (Kruskal-Wallis). Two-way ANOVA was used to compare between-group repeated measures. Statistical significance level was set at .05. The correlation between the size of the mutation and PET parameters and biochemical variables were studied using the linear regression model.
TABLE 1. Clinical Characteristics of Patients With Myotonic Dystrophy

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, y</th>
<th>Sex</th>
<th>PR, s</th>
<th>QRS, s</th>
<th>LVEDD, mm</th>
<th>LVESD, mm</th>
<th>Posterior</th>
<th>Septum</th>
<th>Ejection Fraction, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>47</td>
<td>F</td>
<td>0.20</td>
<td>0.12</td>
<td>44</td>
<td>27</td>
<td>9</td>
<td>8</td>
<td>74</td>
</tr>
<tr>
<td>2</td>
<td>44</td>
<td>M</td>
<td>0.25</td>
<td>0.12</td>
<td>43</td>
<td>27</td>
<td>10</td>
<td>13</td>
<td>72</td>
</tr>
<tr>
<td>3</td>
<td>35</td>
<td>F</td>
<td>0.18</td>
<td>0.08</td>
<td>43</td>
<td>26</td>
<td>10</td>
<td>8</td>
<td>65</td>
</tr>
<tr>
<td>4</td>
<td>31</td>
<td>M</td>
<td>0.20</td>
<td>0.10</td>
<td>64</td>
<td>44</td>
<td>10</td>
<td>11</td>
<td>46</td>
</tr>
<tr>
<td>5</td>
<td>48</td>
<td>M</td>
<td>0.24</td>
<td>0.10</td>
<td>48</td>
<td>33</td>
<td>9</td>
<td>13</td>
<td>58</td>
</tr>
<tr>
<td>6</td>
<td>50</td>
<td>F</td>
<td>0.22</td>
<td>0.12</td>
<td>45</td>
<td>30</td>
<td>10</td>
<td>10</td>
<td>55</td>
</tr>
<tr>
<td>7</td>
<td>38</td>
<td>M</td>
<td>0.24</td>
<td>0.16</td>
<td>54</td>
<td>35</td>
<td>10</td>
<td>13</td>
<td>55</td>
</tr>
<tr>
<td>8</td>
<td>48</td>
<td>M</td>
<td>0.20</td>
<td>0.08</td>
<td>46</td>
<td>30</td>
<td>12</td>
<td>10</td>
<td>63</td>
</tr>
<tr>
<td>9</td>
<td>54</td>
<td>M</td>
<td>0.24</td>
<td>0.06</td>
<td>40</td>
<td>23</td>
<td>10</td>
<td>10</td>
<td>78</td>
</tr>
<tr>
<td>10</td>
<td>49</td>
<td>M</td>
<td>0.24</td>
<td>0.12</td>
<td>50</td>
<td>30</td>
<td>10</td>
<td>10</td>
<td>50</td>
</tr>
<tr>
<td>11</td>
<td>54</td>
<td>F</td>
<td>0.16</td>
<td>0.08</td>
<td>45</td>
<td>28</td>
<td>8</td>
<td>7</td>
<td>67</td>
</tr>
<tr>
<td>12</td>
<td>29</td>
<td>F</td>
<td>0.18</td>
<td>0.09</td>
<td>41</td>
<td>25</td>
<td>7</td>
<td>8</td>
<td>61</td>
</tr>
</tbody>
</table>

LVEDD indicates left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter.

Four patients had both first-degree atrioventricular and complete bundle-branch blocks (patients 2, 6, 7, and 10). Two patients had isolated first-degree atrioventricular block (patients 5 and 9), and one patient had complete bundle-branch block. One patient (4) had dilated left ventricular cavity with normal contraction function.

Results

Table 1 is a summary of main characteristics of patients, including age, sex, PR and QRS durations on a 12-lead ECG, septal and posterior wall thicknesses, and systolic and diastolic diameters on two-dimensional echocardiography. Five patients with DM had first-degree atrioventricular block; of the five, four had left bundle-branch block, and three had isolated left bundle-branch block. Septal and posterior wall thicknesses were normal in all subjects. Only one patient had moderate left ventricular dilation, and none of them had altered left ventricular systolic shortening.

Biological parameters for both patients and control subjects are given in Table 2. Baseline (H0) measurements of glycemia, free fatty acids, lactate, and pyruvate were not statistically different between the two groups, although free fatty acid levels were slightly higher in patients with DM than in control subjects. Plasma levels for insulin were significantly higher in patients than in control subjects. During the glucose loading test, glycemia rose significantly in both groups, as expected. This increase in blood glucose was not different for patients and control subjects. Similarly, free fatty acid, insulin, lactate, and pyruvate variations during the glucose loading test were not statistically different for the two groups.

The rate-pressure product was not different for patients and control subjects at baseline and during PET studies.

Table 3 gives individual values of PET parameters for control subjects and patients. We found a dramatic decrease in MMRGlu in the patients. Similarly, the

TABLE 2. Biological Parameters Recorded Before and After Glucose Loading and After 18F-Fluoro-2-Deoxyglucose

<table>
<thead>
<tr>
<th>Time</th>
<th>Glycemia, mmol/L</th>
<th>Insulinemia, mU/L</th>
<th>Free Fatty Acids, mmol/L</th>
<th>Lactate, mmol/L</th>
<th>Pyruvate, mmol/L</th>
<th>Lactate/Pyruvate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control subjects</td>
<td>H0 5.14 0.37 15.57t 12.20</td>
<td>103.57 12.70</td>
<td>1.03 0.13</td>
<td>91.29 14.38</td>
<td>0.012 0.002</td>
<td></td>
</tr>
<tr>
<td>H1 6.18* 0.37 23.29t 12.21</td>
<td>112.72 12.72</td>
<td>1.00 0.13</td>
<td>92.71 14.38</td>
<td>0.011 0.002</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H2 5.78* 0.37 18.43t 12.19</td>
<td>107.00 12.70</td>
<td>1.91 0.13</td>
<td>100.14 14.38</td>
<td>0.012 0.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients</td>
<td>H0 5.36 0.28 37.13t 9.32</td>
<td>122.00 9.71</td>
<td>1.12 0.10</td>
<td>89.25 10.90</td>
<td>0.014 0.001</td>
<td></td>
</tr>
<tr>
<td>H1 5.93* 0.28 52.58t 9.31</td>
<td>124.83 9.70</td>
<td>1.16 0.10</td>
<td>96.08 10.99</td>
<td>0.014 0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H2 6.16* 0.28 40.00t 9.32</td>
<td>127.17 9.70</td>
<td>1.14 0.10</td>
<td>93.25 10.95</td>
<td>0.013 0.001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Within subjects. tBetween subjects.
Mean±SD values for both control subjects and patients for biological parameters recorded before (H0) and 60 minutes (H1) after glucose loading (50 g PO) and 45 minutes (H2) after 18F-fluoro-2-deoxyglucose injection. Comparisons were made by ANOVA.

During glucose loading, blood levels of glucose increased significantly (vs baseline) in both groups, and the variations were not significantly different between the two groups. Plasma levels of insulin were significantly higher at each time in patients with myotonic dystrophy than in control subjects, and the variations within subjects were not statistically different compared with baseline. Free fatty acid plasma levels were slightly higher in patients than in control subjects; however, the difference failed to reach statistical significance.
phosphorylation rate constant of glucose was significantly lower in patients than in control subjects. However, K1 and k2 rate constants did not differ between patients and control subjects.

No correlation was found between either MMRGlu or k3 and left ventricular ejection fraction, echocardiographic wall thicknesses, left ventricular systolic and diastolic diameters, and PR and QRS durations at ECG in patients.

To assess the possible relation between the length of the CTG repeat and the decreased myocardial glucose phosphorylation observed in patients, Southern blot analysis was performed. The expansion of the (CTG) repeat was investigated in EcoRI digested genomic DNA extracted from lymphocytes of patients with DM by hybridization with cDNA25 (Fig 1). As previously reported,2,3,18-22 a smear of hybridization of the enlarged fragments, reflecting the mitotic instability, was observed. The average size of the amplification varied from ~300 pb to 3500 pb (Table 3).

MMRGlu and k3 were inversely correlated to the size of the DNA mutation (r = -.65 and P = .03, and r = -.85 and P = .001, respectively) (Fig 2). On the other hand, the number of CTG triplet repeats was not linked to the K1 and k2 rate constants, to the biochemical variables, or to the ECG and two-dimensional echocardiogram parameters. Also, neither MMRGlu nor k3 correlated with biochemical, ECG, and echocardiographic variables.

### Discussion

The aim of the present study was to investigate myocardial glucose utilization in patients with DM. We used the method validated by Choi et al15 for estimating the regional parameter of the MMRGlu with PET. This method allows an accurate estimation of myocardial glucose rate even with poor myocardial uptake of FDG.

All subjects were studied under the condition of standardized enhanced myocardial glucose consumption.

We demonstrated that DM is associated with a decrease in myocardial glucose consumption as it has been observed for brain glucose uptake.9 The mechanisms of this reduced myocardial consumption in patients with DM with normal left ventricular function may include

### Table 3. Positron Emission Tomography Kinetic Parameters and Mutation Length

<table>
<thead>
<tr>
<th>Patients</th>
<th>MBF</th>
<th>MMRGlu</th>
<th>k3</th>
<th>K1</th>
<th>k2</th>
<th>FV</th>
<th>Mutation Length</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.67</td>
<td>0.464</td>
<td>0.326</td>
<td>0.274</td>
<td>0.733</td>
<td>0.318</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>0.92</td>
<td>0.816</td>
<td>0.210</td>
<td>0.873</td>
<td>2.160</td>
<td>0.332</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1.02</td>
<td>0.764</td>
<td>0.039</td>
<td>0.135</td>
<td>0.020</td>
<td>0.494</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>0.77</td>
<td>0.713</td>
<td>0.216</td>
<td>0.192</td>
<td>0.369</td>
<td>0.450</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>0.79</td>
<td>0.248</td>
<td>0.657</td>
<td>0.257</td>
<td>4.590</td>
<td>0.383</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>1.00</td>
<td>0.504</td>
<td>0.019</td>
<td>0.153</td>
<td>0.036</td>
<td>0.410</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>0.71</td>
<td>0.986</td>
<td>0.227</td>
<td>0.311</td>
<td>1.041</td>
<td>0.345</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>0.84</td>
<td>0.64</td>
<td>0.24</td>
<td>0.31</td>
<td>1.28</td>
<td>0.39</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>0.14</td>
<td>0.25</td>
<td>0.21</td>
<td>0.26</td>
<td>1.64</td>
<td>0.07</td>
<td></td>
</tr>
</tbody>
</table>

FV indicates left ventricle activity; K1, k2, and k3, blood-to-tissue transfer rate constant, tissue-to-blood transfer rate constant, and glucose phosphorylation rate constant, respectively; and MBF, myocardial blood flow assessed by positron emission tomography and expressed in mL·min⁻¹·cm⁻³ (of myocardial tissue).

Myocardial metabolic rate for glucose (MMRGlu) and k3 in patients with myotonic dystrophy are significantly decreased compared with control subjects (Kruskal-Wallis tests).
decreased MBF, decreased myocardial capillary areas, decreased substrate availability, and primary abnormality of glucose transport across the cell membrane.

MBF was measured using $^{13}$O-labeled water, as previously described and validated. No statistically significant difference for MBF was observed between patients and control subjects in our study. Thereafter, the observed reduced myocardial glucose consumption in patients with DM is not related to impaired MBF. Moreover, since septal and posterior wall thicknesses were normal in all subjects, it seems unlikely that myocardial capillary areas are reduced in patients with DM in our study.

Similarly, since there was no difference between patients and control subjects in plasma levels of glucose and free fatty acid, one can suggest that the energetic substrate delivery to the heart may not be impaired in our patients. The increased plasma levels of insulin that we observed give evidence of whole body insulin resistance in patients with DM as previously described. It should also be emphasized that as far as myocardial oxygen demand is concerned, the rate-pressure product did not differ between patients and subjects.

Consequently, the most probable explanation for decreased glucose consumption by the heart in these subjects is a primary abnormality of glucose utilization by cardiac tissues. A strong decrease in myocardial glucose phosphorylation rate constant occurred in kinetic studies with patients with DM. This latter may explain the reduction in myocardial glucose metabolic rate and is unrelated to myocardial perfusion and energetic substrate delivery to the heart. A fairly large k3 variance was observed in our study, with some control values close to 0. However, our results are conservative in that a smaller data variance and/or higher k3 value in some control subjects would lead to an even more significant difference between control subjects and patients in k3.

The kinetic studies of glucose transport across the cell membrane in the brain showed a reduction in the blood-to-tissue transfer rate constant K1 in patients with DM compared with control subjects. However, in the present study, at the level of the heart the constant K1 did not differ between patients and healthy subjects. Therefore, the impairment of myocardial glucose utilization in DM is not related to an alteration of the rate constant K1. However, the brain phosphorylation rate constant of glucose (k3) is not reduced in patients with DM in the study of Fiorelli et al. The discrepancy between the brain and the heart glucose utilization abnormalities probably results from different carbohydrate metabolism mechanisms. Moreover, the DM mutation displays pronounced heterogeneity in somatic cells. This tissue heterogeneity of the CTG expansion within patients suggests that the correlation between the expansion and k3 should be stronger if cardiac tissue DNA were available for analysis.

The decreased myocardial phosphorylation rate constant of glucose observed in our study may be compared with the impairment of the phosphorylation of erythrocyte membrane proteins previously described in patients with DM. These abnormalities may be related to...
protein kinase defects and are consistent with the recent demonstration of the molecular defect in DM. Indeed, the mutation is an expansion of a CTG trinucleotide repeat in the 3′ untranslated region of a gene encoding a member of the protein kinase family.2,3 In our patients with DM, the reduction in k3 and MMRGluc is inversely linked to the number of CTG triplet repeats. The latter result argues in favor of the primary deficiency in protein kinase activity in the heart, which is responsible for decreased myocardial glucose utilization with increased glucose heart demand. Thus, such an impaired modulation of a protein kinase involved in the activation of the myocardial hexokinase may account for the cardiac manifestation and may provide a pathophysiological schema to relate the molecular defect and the abnormal myocardial metabolism in DM.

Acknowledgments

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