Short-term effects of growth hormone on myocardial glucose uptake in healthy humans

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1Department of Cardiology, Skjby Hospital, University Hospital in Aarhus, DK-8200 Aarhus N; and 2Department of Medicine M (Endocrinology and Diabetes) and 3The PET Centre, Aarhus Kommunehospital, University Hospital in Aarhus, DK-8000 Aarhus C, Denmark

Botker, Hans Erik, Henrik Wiggers, Morten Böttcher, Jens Sandahl Christiansen, Torsten Toftegaard Nielsen, Albert Gjedde, and Ole Schmitz. Short-term effects of growth hormone on myocardial glucose uptake in healthy humans. Am J Physiol Endocrinol Metab 278: E1053–E1059, 2000.—Cardiac muscle is characterized by insulin resistance in specific heart diseases such as coronary artery disease and congestive heart failure, but not in generalized disorders like diabetes mellitus and essential hypertension when cardiac manifestations are absent. To examine whether the insulin antagonistic effect of growth hormone (GH) acts upon the heart, we compared insulin-stimulated whole body and myocardial glucose uptake with and without GH administration during a 3.5-h euglycemic-hyperinsulinemic clamp in eight healthy males. Myocardial 2-deoxy-2-[18F]fluoro-D-glucose uptake was measured with positron emission tomography. The data were converted to myocardial glucose uptake by tracer kinetic analysis. GH did not change the rate-pressure product. GH decreased whole body insulin-stimulated glucose disposal by 26% (48.0 ± 12.1 vs. control 62.8 ± 6.1 µmol·kg⁻¹·min⁻¹, P < 0.02). Free fatty acids were suppressed to a similar extent with and without GH during the insulin clamp. Insulin-stimulated myocardial glucose uptake was similar in the presence and in the absence of GH (0.34 ± 0.05 and 0.31 ± 0.03 µmol·g⁻¹·min⁻¹, P = 0.18). In conclusion, GH does not impair insulin-stimulated myocardial glucose uptake despite a considerable whole body insulin antagonistic effect. Myocardial insulin resistance is not an inherent consequence of whole body insulin resistance.

Myocardial insulin resistance has been demonstrated in patients with specific cardiac manifestations such as coronary artery disease (32) and the cardiac syndrome X (4) but not in patients with generalized disorders like insulin-dependent diabetes mellitus (27, 46) and essential hypertension in the absence of cardiac complications (29). The absence of myocardial insulin resistance in insulin-resistant syndromes has only been found using positron emission tomography (PET) and 2-deoxy-2-[18F]fluoro-D-glucose (FDG) as tracer. However, recent reports suggest that this method may underestimate myocardial glucose uptake in the presence of insulin because disproportionate changes in the uptake of FDG and glucose alter the lumped constant, which is the correction factor that converts myocardial uptake of FDG to myocardial glucose uptake (2, 15).

In the present study, we used PET and a tracer kinetic model that allows determination of individual lumped constants and accurate determination of myocardial glucose uptake by analysis of the myocardial FDG retention curve (2, 3). To establish whether whole body insulin resistance is associated with myocardial insulin resistance in the healthy human heart, we studied whole body and myocardial insulin-stimulated glucose uptake during growth hormone (GH) administration. The insulin antagonistic effects of GH in humans can be traced to skeletal muscle (1, 22), but it is unknown whether it affects myocardial insulin sensitivity. The influence of GH on myocardial glucose uptake is important because it is an approach to induce insulin resistance and thus improves our insight into this condition. In addition, acromegaly and poorly controlled insulin-dependent diabetes mellitus are associated with chronic elevations of circulating GH levels and impaired glucose tolerance. Enhanced cardiac morbidity and mortality characterize these entities, but it is not clear whether this is solely caused by the increased prevalence of coronary artery disease or whether an abnormal myocardial glucose metabolism is involved. Finally, GH has been proposed as a treatment of congestive heart failure, which is per se characterized by insulin resistance (10, 41). The efficacy remains controversial (31, 38), and further insight into the influence of GH on the heart is necessary.

SKELETAL MUSCLE is the major target for insulin-stimulated glucose uptake and the main tissue responsible for reductions in whole body insulin sensitivity in insulin-resistant conditions. Additional organ involvement varies between different insulin-resistant disorders and may include hepatic, neuronal, and cardiac glucose uptake. In the heart, glucose transport is mediated via insulin-sensitive transporter proteins (GLUT-4) similar to those in skeletal muscle (24).

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SUBJECTS AND METHODS

Subjects. Eight healthy male volunteers participated in the study. Their mean ± SD age was 24 ± 3 yr, and their body mass index was 23.7 ± 3.5 kg/m². Blood pressure was 119 ± 12/58 ± 10 mmHg, and resting heart rate was 62 ± 11 beats/min. None had a family history of diabetes, and none was receiving any medication. The local ethics committee approved the study protocol, and all study participants gave informed consent according to the second declaration of Helsinki.

Design. Each participant underwent two randomly sequenced studies with and without GH infusion 2 wk apart. Excessive physical exertion was avoided for 24 h before the examinations. The studies commenced at 8:00 AM after a 10-h overnight fast and were conducted in the supine position. A Venflon catheter was inserted in an antecubital vein for administration of the infusates insulin, glucose, and GH, when given. For blood sampling, a wrist vein of the contralateral hand was cannulated and kept in a heating box to provide arterialized blood. After baseline blood sampling, GH (Norditropin; Novo-Nordisk, Gentofte, Denmark) was infused at a rate of 45 ng·kg⁻¹·min⁻¹ for 5.5 h, whereas control studies were followed by a 2-h rest period before a hyperinsulinemic-euglycemic clamp was performed for the next 3.5 h with a continuous insulin infusion of 1.2 mU·kg⁻¹·min⁻¹. Plasma glucose was measured every 5 min, and euglycemia at 5 mmol/l was maintained by variable amounts of a 20% glucose infusion. The average amount of exogenous glucose required to maintain euglycemia during the final 90 min of the clamp determined whole body insulin sensitivity (M value). Similarly, myocardial insulin sensitivity was determined with PET and FDG as tracer during the last 90 min of the clamp. Blood samples for analysis of glycerol, free fatty acids (FFAs), pyruvate, alanine, GH, and insulin were measured every 30 min during the study. Heart rate and blood pressure were measured every 15 min.

Analytical methods. All samples were analyzed in duplicate. Plasma glucose was measured immediately by a glucose analyzer (Beckman Instruments, Palo Alto, CA). The blood samples were prepared and analyzed for contents in whole blood of lactate and 3-hydroxybutyrate and in plasma for glycerol, FFAs, pyruvate, and alanine, as described earlier (43, 49). In samples stored at −20°C, insulin was analyzed by ELISA using commercial two-site immunonassay (DAKO Diagnostics, Cambridgeshire, UK). GH was measured using an immunofluorometric sandwich assay with two monoclonal antibodies (Delfia hGH; Wallac, Oy, Turku, Finland).

PET. FDG, which we used as tracer for myocardial glucose uptake, was produced by adaptation of a standard procedure using a commercially available device (FDG Microlab; GE Medical Systems, Uppsala, Sweden; see Ref. 45). The specific radioactivity at the end of the synthesis was ≈74 MBq/μmol, and the radiochemical purity exceeded 98%.

We used a whole body PET (ECAT HR 961; Siemens/CTI, Knoxville, TN) with a 15-cm field of view, acquiring 47 transaxial planes with a plane separation of 3.125 mm. Intrinsic in-plane spatial resolution is 3.6 mm full-width half-maximum, and the axial spatial resolution is 3.9 mm. For the final 120 min of the investigation, the study subjects were positioned in the tomograph in the supine position so that the heart and the proximal part of the upper extremities were in the gantry. Before the emission scanning, a 30-min transmission scan was performed for correction of photon attenuation.

Two hours after the insulin infusion was started, and 4 h after the GH infusion was given, 200 MBq of FDG were injected intravenously as a 20-ml bolus over 10–20 s. Dynamic acquisition commenced at the beginning of tracer injection and continued for 90 min to acquire 27 frames (6 × 30 s, 7 × 1 min, 5 × 2 min, 4 × 5 min, and 5 × 10 min). For the analysis of FDG uptake, the PET data were corrected for dead time, decay, and measured photon attenuation. In the analysis of PET images, we used region-of-interest templates. Based on a standard anatomic atlas, three circumferential regions of the left ventricle were identified on the PET images. The region-of-interest templates were applied repetitively to the dynamic imaging sequence to derive tissue time-activity curves for FDG uptake. Averages of the curves from three circumferential regions were used in the fitting procedure. The arterial input function was obtained by placing a small region of interest in the center of the left ventricular blood pool of the static images and copying these regions to the serially acquired images. Drawing small regions of interest approximately four full-width-at-half maximaums away from the cardiac walls minimized spillover into the blood pool. We corrected the myocardial time-activity curves for the effect of partial volume assuming a uniform left ventricular wall thickness of 10 mm (17). This yields a recovery coefficient of 0.73.

Calculation of myocardial glucose uptake. The parameters required for calculation of myocardial glucose uptake from FDG retention were generated by graphical analysis as described by Gjedde (13, 14) and Patlak et al. (33). Corresponding tissue time-activity curves and left ventricular cavity time-activity curves were combined to produce curves representing changes of volume of distribution (VD) as a function of the time integral of left ventricular cavity radioactivity, normalized against that radioactivity (Rt). The curves have a characteristic course that can be described by the equation (50)

\[ V_D = a + \beta (1 - e^{-\gamma t}) \]  

The coefficients, \( \alpha \), \( \beta \), and \( \gamma \) were determined by nonlinear regression. Unidirectional (\( K^\dagger \)) and net (\( K^* \)) clearances of FDG were calculated as

\[ K^\dagger = \alpha + \beta \gamma \]  

and

\[ K^* = \alpha \]  

The rate of myocardial glucose uptake (MGU) was obtained by multiplying \( K^* \) by the plasma glucose concentration ([Glc]p) divided by a lumped constant (LC)

\[ \text{MGU} = K^* \cdot [\text{Glc}]_p / \text{LC} \]  

The lumped constant corrects for all of the kinetic differences between FDG and glucose in the metabolic pathway of transport and phosphorylation. However, the lumped constant is not a true constant but may vary depending on the metabolic environment of the heart (2, 15, 26). We used a specific combination of kinetic rate constants for transport and phosphorylation and the measurable parameters net (\( K^* \)) and unidirectional (\( K^\dagger \)) transport to predict the variable lumped constant. This combination, which we have validated in vivo (2) as well as in vitro (3), allows determination of the lumped constant from the individual FDG time-activity retention curve in specific regions of interest according to the equation

\[ \text{LC} = R_t + (R_t - R_b) K^\dagger / K^\dagger \]
where \( R_p \) is the phosphorylation ratio between FDG and glucose and \( R_t \) is the transport ratio between the unidirectional rates of FDG and glucose transfer over the myocyte membrane. Specific values for \( R_p \) and \( R_t \) are not available for the human heart. We used values for \( R_p = 0.43 \) and \( R_t = 2.26 \) because we have previously found that calculation of myocardial glucose uptake according to Eq. 4 with these values agrees well with global myocardial glucose uptake determined with the Fick principle (2).

Calculations and statistics. Data are presented as means ± SD. The rate-pressure product (RPP) was calculated as heart rate times systolic blood pressure. The RPP values included in the statistical analysis were calculated from six measurements obtained at 15-min intervals during the final 90 min of the dynamic PET scanning. Results were then averaged and included as single values in Wilcoxon’s test for paired differences, which was also used for the other comparative studies of GH effect. Simultaneous comparison of more than two mean values (circulating hormones and metabolites during clamp) was performed with ANOVA for repeated measures followed by a pairwise post hoc t-test modified according to Bonferroni if statistically significant differences were demonstrated. A P value ≤ 0.05 was considered statistically significant.

RESULTS

Whole body glucose uptake. GH decreased the amount of exogenous glucose required to maintain normoglycemia by 26% (48.0 ± 12.1 vs. control 62.8 ± 6.1 µmol·kg⁻¹·min⁻¹, P < 0.02, Fig. 1).

Myocardial glucose uptake. Myocardial glucose uptake was similar in the presence and in the absence of GH (0.34 ± 0.05 and 0.31 ± 0.03 µmol·g⁻¹·min⁻¹, P = 0.20, Fig. 2). GH did not affect the magnitude of the lumped constant (1.12 ± 0.18 and 1.16 ± 0.15, P = 0.61).

Circulating hormones and metabolites. Basal plasma glucose concentrations and plasma glucose concentrations during the clamp were the same with and without GH infusion (Fig. 3). Circulating concentrations of FFAs were similar with and without GH and were equally suppressed throughout the clamp period (Fig. 3). Similar findings were observed for blood 3-hydroxybutyrate and plasma glycerol (data not shown).

Hemodynamics. Heart rate and blood pressure were similar during the control and the GH studies: heart rate 61 ± 9 and 61 ± 7 beats/min (P = 0.76), systolic blood pressure 116 ± 8 and 116 ± 8 mmHg (P = 0.62), and diastolic blood pressure 62 ± 7 and 60 ± 9 mmHg (P = 0.73). Consequently, the rate-pressure product (RPP) did not differ between the control and the GH studies (7,100 ± 1,383 and 7,107 ± 1,151 beats·min⁻¹·mmHg, P = 0.54).

Adverse effects. None of the study participants experienced any adverse effects during GH infusion.

DISCUSSION

The results of the present study show that short-term infusion of GH does not impair insulin-stimulated myocardial glucose uptake despite a generalized insulin antagonistic effect upon glucose uptake in healthy human males. The findings indicate that myocardial insulin resistance is not an inherent consequence of whole body insulin resistance. They also suggest that impaired myocardial glucose utilization is unlikely to be a primary defect in disease states with chronic elevations of circulating GH levels and impaired glucose tolerance, such as acromegaly and poorly controlled diabetes mellitus.

We used GH to study myocardial insulin resistance because the hormone has a documented inhibitory effect on overall glucose uptake in humans (34). Skeletal muscle is the major target organ for the influence of insulin upon glucose uptake. We did not specifically...
study glucose uptake in skeletal muscle in the present study because it is well established that the reduction in whole body insulin sensitivity also after short-term GH administration is caused by an inhibition of glucose uptake mainly in skeletal muscle (1, 22). To obtain this effect, we used the same GH dosage as in the previous studies, and we found a reduction of overall glucose utilization after GH infusion in the same order of magnitude as in these studies. It is well known that GH increases circulating FFA levels in the basal state (23, 30, 35) and that it may increase plasma FFA levels, even during insulin stimulation (1). The substrate competition model of Randle et al. (36) predicts that those elevated levels may inhibit glucose utilization and abolish the effect of insulin on glucose uptake in insulin-sensitive tissues. To ensure suppression of plasma FFA, we used a higher insulin dosage during the hyperinsulinemic-euglycemic clamp than in the previous studies. Although GH-induced lipid mobilization may only be transient (16), we completely avoided a difference in circulating FFAs, excluding any significant role of increased lipid availability for the generation of insulin resistance by GH.

We determined myocardial glucose uptake with FDG and PET. Quantitative assessment of myocardial glucose uptake by FDG has been questioned because the correction factor that equates net myocardial FDG uptake to net myocardial glucose uptake, the so-called lumped constant, is not a true constant (15). The commonly used lumped constant of FDG for the heart is 0.67. However, recent observations both in vitro (15, 26) and in vivo (2) indicate that this correction factor is influenced by modulators of myocardial glucose uptake because of a physiological dependence on membrane transport rates and hexokinase activity (2, 3). As a result of a fixed relation between tracer and tracee for both membrane transport and phosphorylation, we have observed that the magnitude of the lumped constant can be determined individually from the FDG time-activity curve (2, 3). This method was applied in the present study. The constancy of the lumped constant adds support to the finding that GH does not affect membrane transport and hexokinase activity because any factor that changes the activity of the control sites of myocardial glucose uptake would also change the magnitude of the lumped constant (2, 3).

The mechanisms of insulin resistance in skeletal and cardiac muscle are not clear but are thought to involve a defect in membrane transport or the initial intracellular pathways of glycogen formation (1, 7, 39, 51). The glucose transporter proteins GLUT-1 and GLUT-4, which are responsible for glucose transport in skeletal muscle and heart, are similar (24). Stimulation of glucose transport by insulin appears to involve translocation of glucose transporters from an intracellular to a plasma membrane pool in the heart as it does in skeletal muscle (24, 48). However, cardiac glucose metabolism differs from that in skeletal muscle in some respects. First, the rate of insulin-stimulated glucose uptake per muscle weight is at least 10-fold higher in the heart than in resting skeletal muscle (4, 28). Second, the adaptation of myocardial glycogen metabolism to fasting and insulin deficiency differs from that in skeletal muscle. Both fasting (37) and diabetes (8) decrease skeletal muscle glycogen, whereas glycogen increases in cardiac muscle. Third, glucose transport is the major site of control for glucose uptake in skeletal muscle (20) but not in cardiac muscle, where the site of control for glucose uptake shifts between membrane transport and phosphorylation depending on the meta-
bolic influence upon the heart (3). Because GH-induced insulin resistance appears in skeletal but not in cardiac muscle, our results indicate that its impact on insulin sensitivity is localized at a regulatory step that acts differently in the two tissues. Both glucose transport and insulin-sensitive GLUT-4 contents and translocation remain unaffected after GH administration (25, 40, 52), excluding the transport step as the main component in GH-induced insulin resistance. Insulin does not affect the intracellular distribution or the kinetics of hexokinase (9), which made us disregard phosphorylation as a major site of the disturbance. In accordance with previous studies, we suggest that the metabolic disarray induced by GH may be located at the level of glycogen synthesis (16) and may involve mainly glycogen synthase activity in skeletal muscle (1, 5). Our study only assessed the effects of GH on glucose uptake and did not allow us to draw any conclusions about the effect of GH on glucose oxidation and glycogen storage.

Myocardial insulin resistance has been demonstrated in insulin-resistant disorders with specific cardiac diseases such as coronary artery disease (32) and the cardiac syndrome X (4). In disorders with prominent whole body insulin resistance like non-insulin-dependent diabetes mellitus and essential hypertension, myocardial insulin resistance is not observed when cardiac manifestations are absent (29, 46). However, in the presence of concomitant coronary artery disease, patients with non-insulin-dependent diabetes mellitus are also characterized by myocardial insulin resistance (47). Impaired glucose transport in skeletal muscle has recently been identified as a significant cause of decreased insulin-stimulated glycogen synthesis in non-insulin-dependent diabetes (7). Because additional factors may be involved in insulin resistance (39), it is not clear to what extent GH-induced insulin resistance and insulin-resistant disease states are caused by the same underlying mechanisms. The present study confirms that myocardial insulin resistance is not an inherent consequence of whole body insulin resistance, adding further evidence to the assumption that myocardial insulin resistance is a distinct feature of insulin resistance syndromes associated with specific heart diseases. These findings suggest that myocardial insulin resistance may involve other mechanisms than those operating in skeletal muscle.

Disease states with chronic elevations of circulating GH levels and impaired glucose tolerance such as acromegaly and poorly controlled diabetes mellitus may also be associated with cardiac manifestations. Glucose serves as an essential fuel for the myocardium (42). Although the heart is omnivorous in its choice of exogenous substrates for energy production and the relative predominance of one fuel over another depends on the arterial concentration, the use of carbohydrates in contrast to the use of FFA remains significant in the abundance of alternative fuels (42). The importance of impaired myocardial glucose uptake for development of cardiac dysfunction is not known. However, the present study does not point toward impaired myocardial glucose utilization as a major mechanism underlying the cardiac manifestations in disorders with elevated circulating GH levels. Such mechanisms may rather involve premature atherosclerosis (21) and myocyte apoptosis (11).

Experimental studies and some clinical studies have suggested that treatment with recombinant human GH increases left-ventricular mass and improves hemodynamic and functional status in patients with heart failure due to ischemic and dilated cardiomyopathy (10, 12, 19). Although an increase in left-ventricular mass appears to be a consistent finding after weeks of GH treatment, this is not always accompanied by an improvement in clinical status (18, 31). In contrast to a study of healthy males treated with GH for 1 wk (44), we found no immediate hemodynamic effect of GH in the present short-term study. The delay may reflect that myocardial contractility is not augmented by GH per se but by a mechanism involving insulin-like growth factor I, which sensitizes the myofilament to calcium through a wortmannin-sensitive pathway (6). We measured heart rate and blood pressure, which are rather crude measures of hemodynamics. More exact evaluation of hemodynamics is not feasible in healthy human volunteers during PET scanning. Of importance, the measured parameters allowed calculation of RPP, a valid index of cardiac work that was similar with and without short-term GH treatment. Consequently, we could exclude that myocardial metabolism was affected by significant changes in hemodynamics. Further studies are required to clarify whether GH represents a true alternative to existing treatment of congestive heart failure. Although extrapolation to long-term GH exposure should be done with caution, the present study suggests that GH administration is safe and without serious adverse effects on normal human myocardial metabolism.

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