Creatine supplementation may exert beneficial effects on muscle performance and facilitate peripheral glucose disposal in both rats and human subjects. The present study was undertaken to explore the effects of creatine supplementation on the ATP, creatine, phosphocreatine and glycogen content of white and red gastrocnemius and soleus muscles and on blood D-glucose and plasma insulin concentrations before and during an intravenous glucose tolerance test in Goto-Kakizaki rats, a current animal model of inherited type 2 diabetes mellitus. Creatine supplementation increased muscle creatine content, especially in the soleus muscle of young rats (+35.5±15.8%; d.f.=10; p<0.05), and lowered the insulino-genic index, i.e. the paired ratio between plasma insulin and blood D-glucose concentrations. The latter change was mainly attributable to a lowering of plasma insulin concentration. It is proposed, therefore, that creatine supplementation may improve the sensitivity to insulin in extrapancreatic sites in the present animal model of type 2 diabetes.

Abstract. Creatine supplementation may exert beneficial effects on muscle performance and facilitate peripheral glucose disposal in both rats and human subjects. The present study was undertaken to explore the effects of creatine supplementation on the ATP, creatine, phosphocreatine and glycogen content of white and red gastrocnemius and soleus muscles and on blood D-glucose and plasma insulin concentrations before and during an intravenous glucose tolerance test in Goto-Kakizaki rats, a current animal model of inherited type 2 diabetes mellitus. Creatine supplementation increased muscle creatine content, especially in the soleus muscle of young rats (+35.5±15.8%; d.f.=10; p<0.05), and lowered the insulino-genic index, i.e. the paired ratio between plasma insulin and blood D-glucose concentrations. The latter change was mainly attributable to a lowering of plasma insulin concentration. It is proposed, therefore, that creatine supplementation may improve the sensitivity to insulin in extrapancreatic sites in the present animal model of type 2 diabetes.

Introduction

Ever since Hill (1) recognized guanidine-acetate compounds, such as creatine, as a possible tool to study the regulation of glucose homeostasis, many studies have investigated the impact of creatine on carbohydrate metabolism. Creatine intake, commonly used to explore the creatine kinase system in such tissues as skeletal muscle (2,3) and endocrine pancreas (4), increases blood, muscle and pancreas creatine concentration (4,5), and may improve whole body glucose homeostasis (4,6). Theoretically, creatine supplementation could affect tissue glucose uptake either by a direct effect on peripheral tissue, e.g. myocytes, or by increasing pancreatic insulin secretion. It was repeatedly shown that short-term creatine intake not only improves muscular functional capacity (7-10), but also increases muscle glycogen content in rats (11) and humans (6,8,12-14). Moreover, oral creatine intake counteracts the inactivity-induced reduction of muscle GLUT4 expression in healthy volunteers, whilst subsequent rehabilitation training increases muscle GLUT4 content (6,15). However, the effect of creatine intake on insulin secretion remains a matter of debate. Whilst supraphysiological concentrations of guanidino-acetate compounds were found to increase insulin output in some early in vitro studies (16-18), more recent in vivo studies conducted in healthy rats as well as in human subjects failed to confirm these findings (11,14,19-21), except for an increase of fasting insulin levels after 4-8 weeks of creatine supplementation in rats (4).

The above described beneficial action of creatine intake on glucose homeostasis has so far only been documented in healthy rodents and human subjects. Considering its potential clinical therapeutic interest in the prevention and/or treatment of type 2 diabetes, the present study is aimed at investigating whether oral creatine supplementation has an impact on whole body glucose disposal during an intravenous glucose tolerance test in Goto-Kakizaki rats, a current animal model of inherited type 2 diabetes (22). Moreover, in order to explore possible age-related differences in the response to creatine supplementation, the experiments were conducted in either 6-week or 14-week old animals.

Materials and methods

Animals. Male Goto-Kakizaki (GK) rats, obtained from a colony bred at Brussels Free University, were maintained on a 12:12 light-dark cycle at 22°C. From the start of the study, 6-week (n=12) and 14-week (n=12) old GK rats were caged individually and allowed, for 8 successive weeks, free access to normal rodent pellets (Kliba Nafag, Kaiseraugust, Switzerland) alone (control group) or enriched with 2% (w/w) creatine monohydrate (Creapure®, Degussa, Freising, Germany; creatine group). All rats had free access to drinking water. The study protocol was approved by the Ethics Committee for Animal Procedures at K.U. Leuven.
Study protocol. Following the above described dietary interventions, rats were anaesthetized intraperitoneally with a mixture of ketamine (50 mg/kg⁻¹; Pfizer, Brussels, Belgium), xylazine (10 mg/kg⁻¹; Bayer, Leverkusen, Germany) and atropine (0.25 mg/kg⁻¹; Sterop Brussels, Belgium) and were prepared surgically for an intravenous glucose tolerance test. Briefly, this involved catheter (Degania Silicone, Degania Bet, Israel) insertion into the left vena jugularis, and tunneling to an incision in the neck. To avoid clotting, the silicone catheter was filled with heparinized saline before sealing. After an overnight fast (16-18h), a 150 μl blood sample was collected from the tail tip in heparinized capillaries. Blood glucose concentration was measured immediately in duplicate. The remainder of the blood sample was rapidly centrifuged (13,000 x g at 4°C, 3 min) and the supernatant was stored at -80°C for plasma insulin analysis at a later date. Thereafter, conscious rats were injected with 1 g glucose/kg⁻¹ body weight using a 30% (w/v) D-glucose solution in 0.9% (w/v) saline. Following 5, 10, 15, 30, 60, 90 and 120 min, blood samples were collected and processed as described above. After blood sampling, the rats were anaesthetized intravenously using pentobarbital sodium (0.5 mg/kg⁻¹; Nembutal, Brussels, Belgium). The medial superficial part of the gastrocnemius consisting mainly of fast-glycolytic fibers (white gastrocnemius), the soleus consisting mainly of slow-oxidative fibers and a deep part of the medial head of the gastrocnemius consisting mainly of fast-oxidative fibers (red gastrocnemius) were dissected from both hind limbs, freed from visible connective tissue and blood, freeze-clamped with aluminium clamps cooled in liquid N₂ and stored at -80°C for analysis at a later date. The rats were then sacrificed by pentobarbital sodium overdose.

Measurements
Food intake and body weight. Following 8 weeks of ad libitum access to the described rat pellets, residual food was weighed to calculate average daily food intake. Body weight was registered on a weekly basis.

Blood biochemistry. Whole blood glucose concentration was determined in duplicate on an Analox® GM7 glucose analyzer (London, England). Plasma insulin concentration was determined by a double-antibody radio-immunoassay with rat insulin as the standard (Novo Research Institute, Bagsvaerd, Denmark).

Muscle biochemistry. For the biochemical analysis, muscle samples from the right hind limb were freeze-dried for 36 h at -50°C. Muscle glycogen content of the freeze-dried muscle samples (2-3 mg) was determined fluorometrically by a hexokinase method after acid hydrolysis (23). Muscle ATP, free creatine and phosphocreatine concentration was analyzed from perchloric acid precipitated extractions of the freeze-dried muscle samples (3-5 mg) using standard enzymatic fluorometric assays (24). Muscle total creatine content was calculated as the sum of free creatine and phosphocreatine. All data are expressed in mmol/kg⁻¹ dry weight (wt.).

Statistical analysis. The insulinogetic index was taken as the paired ratio between plasma insulin and blood glucose concentration. During the intravenous glucose tolerance test, two older creatine-supplemented rats died for an unknown reason. They were excluded from all statistical analyses. All results are expressed as mean values (± SEM). The statistical significance of differences between mean values was assessed, as required, by variance analysis or use of Student’s t-test.

Results
Body weight and food intake. Fig. 1 illustrates the time course for the changes in body weight in the four groups of rats. Over a period of 8 weeks, the gain in body weight was not different (P>0.25 or more) in the control and creatine-supplemented rats (Table I). It was obviously higher (P<0.001) in the younger rats (167±6 g; n=12) than in the older animals (48±3 g; n=12). As expected, however, it was slightly higher (P<0.02) in the older rats (25.5±0.6 g/day; n=6) than in the younger animals (23.4±0.4 g/day; n=6).

Blood D-glucose and plasma insulin concentrations. The basal blood D-glucose concentration, after overnight fasting, was not different in control and creatine-supplemented rats at 14 or 22-23 weeks of age (Table I). It was significantly higher (P<0.05), however, in the older rats (8.23±1.84 mM; n=10) than in the younger animals (4.24±0.13 mM; n=12). Five minutes after the intravenous injection of D-glucose, the increment in blood D-glucose concentration above paired basal value was not significantly different in younger versus older rats and in control versus creatine-supplemented animals, with an overall mean value of 8.42±0.45 mM (n=22). Thereafter, the blood D-glucose concentration remained fairly stable, clearly documenting glucose intolerance in the GK rats. Even at 120 min, the paired decrease in blood D-glucose
concentration below that recorded at 5 min did not exceed 2.21±0.52 mM (n=22). In this respect, there was again no significant difference between younger and older rats or control and creatine-supplemented animals (Table I).

The increase in blood D-glucose concentration provoked by the injection of the hexose was not associated with any sizeable increase in plasma insulin concentration. On the contrary and as a rule, the concentration of insulin was somewhat lower after than before exogenous D-glucose administration (Fig. 2). Both before and after such administration, the mean plasma insulin concentration was higher in older than younger rats. Thus, in the latter animals, it averaged 148.1±11.7% (n=36; P<0.001) of the corresponding mean values found at the same time during the glucose tolerance test in younger rats fed the same diet (100.0±4.5%; n=48). The higher plasma insulin concentration found in older compared to younger animals coincided, as already mentioned, with a higher blood D-glucose concentration in the former. In both younger and older rats, the plasma insulin concentration was lower in the creatine-supplemented animals than in the control ones; pooling all available data, it averaged, in the creatine-supplemented animals, 81.2±3.4% (n=40; P<0.05) of the mean corresponding values found at the same time during the glucose tolerance test and at the same age in control rats (100.0±7.5%; n=44). When considering young and older rats on a separate basis, such a difference remained significant (P<0.025) only in the younger animals. Nevertheless, the percentage found in the creatine-supplemented animals was not significantly different (P>0.5) in young rats (79.3±4.4%; n=24) and older rats (83.9±5.4%; n=16), both of these values being significantly lower (P<0.01 or less) than unity.

**Insulinogenic index.** The finding that creatine supplementation lowers the plasma insulin, but not blood D-glucose, concentration could suggest improved sensitivity to insulin in extrapancreatic site(s). This consideration led us to establish the insulinogenic index, i.e. the paired ratio between plasma insulin and blood D-glucose concentrations.

The insulinogenic index was lower in the creatine-supplemented GK rats than in the control animals (Fig. 3, middle panel). The relative magnitude of such a decrease was not significantly different (d.f.=38; P>0.2) in the animals examined at the age of either 14 or 23 weeks. Thus, relative to the mean values found at the same time(s) during the glucose tolerance test in the control animals, the measurements made in the creatine-supplemented rats averaged, at the 14th and 22nd and 23rd week, 77.9±4.7% (n=24) and 68.3±6.3% (n=16), respectively. Pooling all available data, the insulinogenic index averaged, in the creatine-supplemented rats, 74.2±3.8% (n=40; P<0.01) of the mean corresponding control values (100.0±8.6%; n=44). It should be emphasized that, relative to the mean value found at the same age in the control rats, the insulinogenic index measured in the creatine-supplemented

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**Table I.** Body weight change, food intake and blood D-glucose concentration.

<table>
<thead>
<tr>
<th>Age (weeks)</th>
<th>14</th>
<th>22-23</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diet</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body wt. gain (g/8 weeks)</td>
<td>169±11 (6)</td>
<td>165±4 (6)</td>
</tr>
<tr>
<td>Food intake (g/day)</td>
<td>23.1±0.9 (3)</td>
<td>23.7±0.4 (3)</td>
</tr>
<tr>
<td>Blood D-glucose (mM)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>basal</td>
<td>4.19±0.22 (6)</td>
<td>4.28±0.18 (6)</td>
</tr>
<tr>
<td>Δ (min 5-min 0)</td>
<td>9.02±0.41 (6)</td>
<td>8.23±0.42 (6)</td>
</tr>
<tr>
<td>Δ (min 5-min 120)</td>
<td>1.93±1.30 (6)</td>
<td>1.71±0.91 (6)</td>
</tr>
</tbody>
</table>
rats was not significantly different (d.f.=38; P>0.6) before exogenous D-glucose administration (70.7±7.1%; n=10) and at identical time(s) thereafter (75.2±4.5%; n=30).

The administration of D-glucose always caused a dramatic decrease in the insulinogenic index (Fig. 3, upper panel). The relative magnitude of such a glucose-induced decrease in the insulinogenic index was not significantly different in control rats and creatine-supplemented animals (Fig. 3, lower panel).

When comparing the rats examined at 14 and 22-23 weeks of age, the relative magnitude of the glucose-induced decrease in the insulinogenic index was, at each time of the test, more pronounced in the younger rats than in the older animals (Fig. 3, lower panel). Thus, relative to paired basal value, the insulinogenic index recorded after intravenous injection of D-glucose averaged 44.7±4.4% (n=27) in the 22- to 23-week old rats, compared to (P<0.001) only 29.2±1.8% (n=36) in the 14-week old animals. When compared at the same time of the test (10, 30 and 90 min), the mean percentage reached in the younger rats only represented 65.4±3.7% (n=36; P<0.001) of that recorded in the older animals (100±9.6 %; n=27).

This coincided, however, with the fact already mentioned that the mean basal blood D-glucose concentration was lower (P<0.05) in the 14-week old rats (4.24±0.13 mM; n=12) than in the animals examined at the age of 22-23 weeks, whether considering all of the latter animals (8.23±1.84 mM; n=10) or only those in which the plasma insulin concentration was measured (8.11±2.05 mM; n=9). There was indeed a highly significant correlation (r=0.7782; n=21; P<0.001) between the individual measurements of basal blood D-glucose concentrations and the corresponding mean value for the insulinogenic index recorded after administration of exogenous D-glucose and expressed relative to paired basal value (Fig. 4, lower panel). The upper panel of Fig. 4 illustrates the progressive increase in the mean values for the insulinogenic index measured after intravenous administration of D-glucose and expressed relative to paired basal value as a function of the basal plasma D-glucose concentration. It reveals that such an increase already achieved statistical significance in the lowest range of basal plasma D-glucose concentrations recorded in the present study.
Muscle biochemistry. Table II summarizes the data relative to muscle biochemistry. The mean values for ATP, phosphocreatine and total creatine content, paired phosphocreatine/creatine ratio and glycogen content were always lower in the soleus muscle than in the gastrocnemius muscles. Pooling all available data, the ATP content, phosphocreatine and total creatine content, paired phosphocreatine/creatine ratio and glycogen content of the soleus muscle averaged 72.1±2.9%, 66.1±2.6%, 73.6±2.2%, 71.4±3.4% and 78.3±4.0% (n=22 in all cases), respectively, of the mean paired values (100.0±1.4%; n=41; 100.0±2.5%, n=41; 100.0±1.8%, n=41; 100.0±3.5%, n=41; and 100.0±1.4%, n=44) found in the two gastrocnemius muscles (Fig. 5). Such differences were all highly significant (P<0.001). For these five percentages, there was, as a rule, no significant difference in the soleus muscle of younger versus older rats or control versus creatine-supplemented animals. Only the mean percentage concerning the glycogen content of the soleus muscle was higher (P<0.01) in the older rats (89.7±3.4%; n=10) than in the younger animals (68.8±5.5%; n=12). There was no significant difference, in terms of ATP or glycogen content between white and red gastrocnemius muscles. The phosphocreatine content, total creatine content and paired phosphocreatine/creatine ratio averaged in the white gastrocnemius muscle respectively 107.1±3.3, 104.3±2.4 and 109.5±4.7% (n=20 in all cases), compared to 93.2±3.1, 95.9±2.3 and 91.0±4.5% (n=21 in all cases) in the red gastrocnemius muscle.

Non-phosphorylated creatine content of the soleus muscle averaged 92.9±3.8% (n=22) of the mean paired value measured in the two gastrocnemius muscles (100.0±2.4%; n=44). These two percentages were not significantly different from one another (P>0.1). Likewise, as judged from the same normalized data, the creatine content of the white gastrocnemius (98.0±3.4%; n=22) was not significantly different (P>0.4) to that of the red gastrocnemius (102.0±3.4%; n=22).

Two obvious age-related differences in muscle biochemistry consisted of the increase (P<0.001) in the soleus glycogen content from 87.4±6.2 nmol/kg⁻¹ (n=12) in the 14-week old rats to 130.4±5.7 nmol/kg⁻¹ (n=10) in the 22- to 23-week old rats, and the decrease (P<0.02) in the soleus phosphocreatine/creatine ratio from 2.36±0.19 (5) to 1.76±0.28 (6) in the white gastrocnemius muscle.

### Table II. Muscle biochemistry.

<table>
<thead>
<tr>
<th>Age (weeks)</th>
<th>Diet</th>
<th>Control</th>
<th>Creatine</th>
<th>Control</th>
<th>Creatine</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td>White gastrocnemius</td>
<td>28.6±1.0 (5)</td>
<td>27.0±3.5 (6)</td>
<td>26.1±2.0 (5)</td>
<td>27.1±1.8 (4)</td>
</tr>
<tr>
<td></td>
<td>Red gastrocnemius</td>
<td>27.5±1.4 (6)</td>
<td>28.4±1.8 (5)</td>
<td>24.6±2.1 (6)</td>
<td>27.8±1.9 (4)</td>
</tr>
<tr>
<td></td>
<td>Soleus</td>
<td>20.1±1.5 (6)</td>
<td>21.9±3.0 (6)</td>
<td>18.7±1.0 (6)</td>
<td>16.2±1.2 (4)</td>
</tr>
<tr>
<td>22-23</td>
<td>White gastrocnemius</td>
<td>33.7±3.1 (6)</td>
<td>42.8±4.3 (6)</td>
<td>49.9±3.4 (6)</td>
<td>47.5±6.9 (4)</td>
</tr>
<tr>
<td></td>
<td>Red gastrocnemius</td>
<td>38.7±2.6 (6)</td>
<td>42.9±7.4 (6)</td>
<td>48.5±4.7 (6)</td>
<td>53.8±3.6 (4)</td>
</tr>
<tr>
<td></td>
<td>Soleus</td>
<td>32.3±1.6 (6)</td>
<td>43.7±4.8 (6)</td>
<td>42.6±3.8 (6)</td>
<td>44.3±2.5 (4)</td>
</tr>
<tr>
<td></td>
<td>White gastrocnemius</td>
<td>117.3±5.6 (5)</td>
<td>112.0±11.0 (6)</td>
<td>95.5±10.9 (5)</td>
<td>110.3±11.6 (4)</td>
</tr>
<tr>
<td></td>
<td>Red gastrocnemius</td>
<td>89.1±5.4 (6)</td>
<td>85.7±13.1 (5)</td>
<td>99.0±7.5 (6)</td>
<td>99.6±1.5 (4)</td>
</tr>
<tr>
<td></td>
<td>Soleus</td>
<td>70.9±2.9 (6)</td>
<td>71.0±10.7 (6)</td>
<td>59.1±2.7 (6)</td>
<td>65.4±5.9 (4)</td>
</tr>
<tr>
<td></td>
<td>White gastrocnemius</td>
<td>148.5±5.7 (5)</td>
<td>154.8±10.9 (6)</td>
<td>145.7±9.7 (5)</td>
<td>157.8±12.3 (4)</td>
</tr>
<tr>
<td></td>
<td>Red gastrocnemius</td>
<td>127.8±6.3 (6)</td>
<td>131.1±15.3 (5)</td>
<td>147.4±10.4 (6)</td>
<td>153.4±4.0 (4)</td>
</tr>
<tr>
<td></td>
<td>Soleus</td>
<td>103.2±2.8 (6)</td>
<td>114.7±9.6 (6)</td>
<td>101.6±5.5 (6)</td>
<td>109.7±7.9 (4)</td>
</tr>
<tr>
<td></td>
<td>White gastrocnemius</td>
<td>3.85±0.38 (5)</td>
<td>2.74±0.32 (6)</td>
<td>1.99±0.29 (5)</td>
<td>2.52±0.52 (4)</td>
</tr>
<tr>
<td></td>
<td>Red gastrocnemius</td>
<td>2.36±0.19 (6)</td>
<td>2.25±0.52 (5)</td>
<td>2.11±0.24 (6)</td>
<td>1.88±0.14 (4)</td>
</tr>
<tr>
<td></td>
<td>Soleus</td>
<td>2.23±0.16 (6)</td>
<td>1.76±0.28 (6)</td>
<td>1.44±0.14 (6)</td>
<td>1.47±0.09 (4)</td>
</tr>
<tr>
<td></td>
<td>White gastrocnemius</td>
<td>132.3±8.8 (6)</td>
<td>136.0±12.2 (6)</td>
<td>146.5±8.8 (6)</td>
<td>145.4±5.2 (4)</td>
</tr>
<tr>
<td></td>
<td>Red gastrocnemius</td>
<td>141.8±17.7 (6)</td>
<td>109.7±11.2 (6)</td>
<td>150.5±7.4 (6)</td>
<td>138.5±6.2 (4)</td>
</tr>
<tr>
<td></td>
<td>Soleus</td>
<td>88.6±7.4 (6)</td>
<td>86.3±10.7 (6)</td>
<td>134.8±9.0 (6)</td>
<td>123.9±4.1 (4)</td>
</tr>
</tbody>
</table>
As a rule, there was no significant difference in the variables of muscle biochemistry between control and creatine-supplemented animals. Nevertheless, the creatine content of the muscles averaged, in the former case 129.4±6.3% (n=20) of the mean corresponding value found in the latter (100.0±4.3%; n=24). This coincided, in the red gastrocnemius muscle, with a significantly higher total creatine content in older than younger rats, averaging in the former case 116.1±6.0% (n=30; P<0.05) of the mean corresponding value found at the same age in the control rats (100.0±4.8%; n=24). In the case of the fast glycolytic white and fast oxidative red gastrocnemius muscles, however, the value found in the creatine-supplemented rats (112.7±7.5%; n=20) failed to be significantly higher (P>0.1) than that found at the same age in the control animals (100.0±3.8%; n=24). In the present work, creatine supplementation was continued for 8 weeks because acute creatine intake was found not to alter glucose tolerance or insulin sensitivity (20). Our current findings are compatible with the literature data indicating that a higher level of muscle total creatine content established by acute creatine intake is not maintained upon prolonged supplementation (26).

Second, it reveals that creatine supplementation lowers the insulinogenic index in GK rats. This decrease was observed in both younger and older animals and both before and after administration of exogenous D-glucose (Fig. 3). It was mainly attributable to a lowering of the plasma insulin concentration. These findings suggest, therefore, that creatine supplementation increased the sensitivity to insulin at extrapancreatic sites, possibly including skeletal muscles. However, contradicting the beneficial effect of creatine on muscular insulin sensitivity is the observation that dietary creatine administration did not increase the sensitivity to insulin at extrapancreatic sites.

Finally, the measurements of blood D-glucose and plasma insulin concentration made in the intravenous glucose tolerance test indicated that the severe intolerance to sugar found in GK rats coincided with a paradoxical decrease in plasma insulin concentration and insulinogenic index. Such a paradoxical secretory response of insulin-producing cells in response to...
provoked hyperglycemia, which was already documented in the isolated perfused pancreas of GK rats (27,28), is currently considered as one of the two typical features of the phenomenon of so-called B-cell glucotoxicity or incompetence (29). In this respect, the following considerations should be emphasized.

The relationship illustrated in Fig. 4 between basal plasma D-glucose concentration and the relative magnitude of this glucose-induced paired decrease in the insulinogenic index during the intravenous glucose tolerance test reinforces the view that the paradoxical lowering of such an index, as provoked by the administration of exogenous D-glucose, may be attributable to the interference of the rise in glyceremia, following the injection of the hexose, with the catabolism of endogenous nutrients in the insulin-producing cells, such as a decrease in the rate of glycolysis (30,31). It may indeed be expected that such a rate is already lower in severely hyperglycemic, as compared to close-to-normoglycemic, rats before the administration of exogenous D-glucose and, hence, less susceptible to a further decrease in response to the rise in glyceremia provoked by the injection of the hexose in the former, as compared to the latter, animals. This is not to deny that the extent of glycogen accumulation in insulin-producing cells is probably related to the severity and duration of the perturbation in glucose homeostasis before the injection of exogenous D-glucose, as documented in prior studies (32,33).

It should also be kept in mind that, in overnight fasted rats, the increase in the rate of exogenous D-glucose utilization in islet B-cells is lower than in fed animals (34). Since such a fasting-induced change in D-glucose catabolism, as resulting mainly from the change in activity of key glycolytic enzymes (35), appears attributable to the lowering of plasma D-glucose concentration during starvation, it may also be expected to be most pronounced in rats with the lowest basal glyceremia. This would then, in turn, also contribute to a lower insulin response during the glucose tolerance test in these rats, as compared to animals that remained frankly hyperglycemic, even after overnight fasting.

In conclusion, the present study reinforces the concept that the secretory responsiveness of insulin-producing B-cells to a hyperglycemic challenge is modulated, in the present animal model of type 2 diabetes, by the preceding glyceremic status. It also reveals that creative supplementation lowers the insulinogenic index in GK rats, both before and after the administration of exogenous D-glucose. In the light of prior findings (6,21), this may well correspond with the improvement in insulin sensitivity in extrapancreatic targets, e.g. muscle, resulting from the administration of creatine in diabetic GK rats.

Acknowledgements

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