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Preferential alteration of oxidative relative to total glycolysis in pancreatic islets of two rat models of inherited or acquired Type 2 (non-insulin-dependent) diabetes mellitus

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Summary. In islets from both adult rats injected with streptozotocin during the neonatal period and spontaneously diabetic rats obtained by repeated selective breedings (GK rats), the ratio between D-[3, 4-^{14}C]glucose oxidation and D-[5-^{3}H]glucose conversion to ^{3}HOH was 25 % lower than in islets from control rats, indicating an impaired contribution of oxidative to total glycolysis. No primary defect in the Krebs cycle was found in the islets of diabetic rats, as judged from the ratio between either D-[2-^{14}C]glucose or D-[6-^{14}C]glucose and D-[3, 4-^{14}C]glucose oxidation. Therefore, we propose that a preferential alteration of oxidative glycolysis in the pancreatic beta cell may contribute to the impairment of glucose-induced insulin release not only in a cytotoxic but also in a spontaneous model of non-insulin-dependent diabetes mellitus.

Key words: Pancreatic islets, GK rats, streptozotocin, glucose metabolism.

The impairment of glucose-induced insulin release in non-insulin-dependent diabetes mellitus has been suggested to be caused by a defect of D-glucose transport across the islet beta-cell plasma membrane [1, 2]. It is also conceivable, however, that such an impairment is due to a more distal anomaly in D-glucose metabolism, *e.g.* at the level of its phosphorylation or oxidative catabolism. The present report reveals that, in two experimental models of non-insulin-dependent diabetes, namely in adult rats injected with streptozotocin during the neonatal period (STZ rats) and in spontaneously glucose-intolerant rats [3, 4] obtained by selective breeding over numerous generations (GK rats), the oxidation of D-[3, 4-^{14}C]glucose by pancreatic islets is impaired even when expressed relative to total glycolytic flux. Therefore, we propose that a perturbation of mitochondrial oxidative events, rather than hexose transport, plays an essential role in the secretory defect.

Materials and methods

Control Wistar rats, animals injected with STZ [5] during the neonatal period (STZ rats) and GK rats [6] were given free access to food [7]. The rats were weighed and then decapitated. Blood was collected in heparinized tubes for the measurement of plasma glucose by the glucose oxidase method [8] and plasma insulin by radioimmunoassay [9]. In each experiment, islets were isolated by the collagenase method [10] from the pancreas of two rats in each group. Two groups of ten islets each were used for the measurement of islet protein and insulin content [10, 11]. For the measurement of ^{14}C-labelled D-glucose oxidation and D-[5-^{3}H]glucose utilization, groups of ten islets each were incubated for 120 min at 37 °C in 40 µl of a bicarbonate-buffered medium [10] containing bovine serum albumin (5 mg/ml). In some experiments, the incubation medium was deprived of $CaCl_2$ and contained 0.5 mmol/l EGTA. The production of $^{14}CO_2$ and ^{3}HOH was measured as previously described [12]. The acidified medium containing the islets was stored at −20 °C and later examined for its content in ^{14}C-labelled amino acids and acidic metabolites separated by ion-exchange chromatography [13, 14].

Statistical analysis

All results were expressed as mean ± SEM, together with the number of individual observations (n), and were compared using Students unpaired t-test.

Results

Metabolic and hormonal status

The GK rats were somewhat older ($p < 0.001$) and, yet, displayed a lower body weight ($p < 0.05$) than the control and STZ rats (Table 1). In the fed state, the plasma glucose concentration was higher ($p < 0.01$) in STZ and GK than control rats. The plasma insulin concentration was not significantly different among the three groups of rats.

Table 1. Metabolic and hormonal status of control rats, animals injected neonatally with streptozotocin (STZ) and GK rats

Rats	Control	STZ	GK
Age (days)	96.5 ± 0.3	96.5 ± 0.3	119.5 ± 0.3
Body weight (g)	360.5 ± 18.6	367.3 ± 13.9	314.5 ± 16.9
Plasma glucose (mmol/l)	7.62 ± 0.19	9.62 ± 0.33	9.41 ± 0.69
Plasma insulin (μU/ml)	71 ± 9	67 ± 1	88 ± 20
Plasma insulin/ glucose (U/mol)	9.3 ± 1.3	6.8 ± 0.1	9.2 ± 1.8
Islet insulin (μU/islet)	954 ± 42	346 ± 71	405 ± 58
Islet protein (μg/islet)	0.85 ± 0.15	0.93 ± 0.20	0.59 ± 0.10
Islet insulin/protein (mU/μg)	1.23 ± 0.20	0.47 ± 0.16	0.74 ± 0.19

Mean values (± SEM) refer to four or more individual observations

The mean plasma insulin/glucose ratio was decreased ($p < 0.10$) only in the STZ rats. The insulin content of the islets was severely decreased in both STZ and GK rats ($p < 0.001$). The islet protein content was not affected in STZ rats and slightly but not significantly lower in GK than control rats. The insulin/protein islet content was significantly decreased in STZ rats ($p < 0.03$), but not ($p > 0.16$) in GK rats. When considering the latter findings, it should be noted that only well-identified, relatively large islets were collected from either control or diabetic rats.

D-[5-^{3}H]glucose conversion to ^{3}HOH

As judged from the conversion of D-[5-^{3}H]glucose to ^{3}HOH, the rate of glycolysis was not significantly different in control and STZ rats (Table 2). In the GK rats, the glycolytic flux, when expressed per islet, was lower than the control value ($p < 0.001$) only at a high concentration of D-glucose (16.9 mmol/l). This difference was no longer observed, however, when the rate of glycolysis recorded in the presence of 16.9 mmol/l D-glucose was expressed relative to the islet protein content. The results then averaged 250.7 ± 11.7 and 252.2 ± 20.5 pmol/120 min per μg in control and GK rats, respectively.

The relative magnitude of the increase in glycolysis attributable to a rise in the D-glucose concentration was less marked in STZ and GK than control rats. Thus the 16.9 mmol/l to 5.1 mmol/l ratio in ^{3}HOH production averaged 2.11 ± 0.13 in STZ rats and 2.08 ± 0.16 in GK rats, as compared ($p < 0.02$ or less) to 2.61 ± 0.14 in control animals.

At 16.9 mmol/l D-glucose, the mean production of ^{3}HOH from D-[5-^{3}H]glucose was always slightly lower in the absence than presence of Ca^{2+}, but this difference failed to achieve statistical significance.

D-[3, 4-^{14}C]glucose oxidation

To avoid the interference of differences in islet size, all oxidative data were expressed relative to the paired production of ^{3}HOH from D-[5-^{3}H]glucose. The oxidation of D-[3, 4-^{14}C]glucose will be considered first as it provides information concerning the rate of oxidative glycolysis as coupled to the decarboxylation of pyruvate in the reaction catalysed by pyruvate dehydrogenase [14].

In either control, STZ or GK rats, a rise in D-glucose concentration from 5.1 to 16.9 mmol/l increased the oxidation of D-[3, 4-^{14}C]glucose relative to the utilization of D-[5-^{3}H]glucose (Table 2). By comparing the data collected within each experiment, such an increase was most obvious in control rats ($p < 0.001$), still evident in STZ rats ($p < 0.03$), but of doubtful significance ($p < 0.08$) in GK rats. At the high hexose concentration, the mean ratio between D-[3, 4-^{14}C]glucose oxidation and D-[5-^{3}H]glucose utilization was lower in the absence than presence of extracellular Ca^{2+}. Once again, such a difference was highly significant ($p < 0.01$) in control rats, whilst failing to achieve statistical significance in either STZ or GK rats.

Most importantly, the absolute values for the paired ratio between D-[3, 4-^{14}C]glucose oxidation and D-[5-^{3}H]glucose utilization were much lower ($p < 0.01$) in STZ or GK than control rats, whether at low or high concentration of D-glucose or in the presence or absence of Ca^{2+}. Pooling all available data, such a ratio averaged in STZ and GK rats, respectively, 74.4 ± 2.7 and 72.7 ± 3.2 % ($p < 0.001$ in both cases) of the corresponding mean value found in control rats (100.0 ± 2.4 %; n = 27 to 35).

A comparable trend was observed for ^{14}C-labelled amino acids generated from D-[3, 4-^{14}C]glucose. Thus, when expressed relative to the paired formation of ^{3}HOH from D-[5-^{3}H]glucose, the production of ^{14}C-labelled amino acids, which correspond mainly to the net generation of L-[1-^{14}C]alanine [14], averaged in the STZ and GK rats, respectively, 76.0 ± 11.0 % (n = 17) and

Table 2. D-glucose metabolism in islets from control rats, animals injected neonatally with streptozotocin (STZ) and GK rats

Rats (Type)	D-glucose (mmol/l)	Ca^{2+} (mmol/l)	D-[5-^{3}H]glucose to ^{3}HOH (pmol/120 min per islet)	D-glucose oxidation/D-[5-^{3}H]glucose utilization (%)		
				D-[3,4-^{14}C]glucose	D-[6-^{14}C]glucose	D-[2-^{14}C]glucose
Control	5.1	1.0	81.2 ± 4.8 (36)	60.0 ± 3.2 (11)	20.4 ± 1.0 (12)	42.4 ± 2.1 (12)
	16.9	1.0	212.1 ± 9.9 (35)	77.0 ± 2.6 (12)	26.8 ± 0.6 (12)	51.9 ± 2.1 (11)
	16.9	Nil	194.9 ± 13.2 (36)	65.6 ± 2.8 (12)	20.1 ± 0.5 (12)	46.7 ± 2.9 (12)
STZ	5.1	1.0	95.9 ± 7.5 (35)	43.2 ± 3.3 (11)	19.7 ± 1.1 (11)	36.4 ± 1.8 (12)
	16.9	1.0	204.7 ± 16.1 (36)	55.2 ± 3.7 (11)	21.0 ± 0.8 (12)	47.3 ± 2.5 (12)
	16.9	Nil	181.5 ± 9.9 (36)	47.9 ± 2.3 (12)	18.0 ± 0.4 (12)	33.7 ± 1.8 (12)
GK	5.1	1.0	74.4 ± 5.6 (27)	43.0 ± 3.4 (9)	11.4 ± 0.7 (9)	36.8 ± 3.9 (9)
	16.9	1.0	148.8 ± 12.1 (27)	53.1 ± 4.1 (9)	21.4 ± 1.1 (9)	57.4 ± 6.5 (9)
	16.9	Nil	135.6 ± 10.9 (27)	50.8 ± 4.0 (9)	14.2 ± 2.5 (9)	35.9 ± 2.0 (9)

$73.9 \pm 10.6\%$ ($n = 13$) of the mean corresponding value found within the same experiments and under the same incubation conditions in control rats ($100.0 \pm 12.0\%$; $n = 18$). In the latter animals, the absolute value for the paired ratio between the generation of ^{14}C-labelled amino acids from D-[3, 4-^{14}C]glucose and the utilization of D-[5-^{3}H]glucose averaged $7.9 \pm 1.2\%$ in the presence of Ca^{2+} and at high hexose concentration (16.9 mmol/l). Whether in control, STZ or GK rats, such a paired ratio was higher at 5.1 than 16.9 mmol/l D-glucose. In the presence of Ca^{2+} and at 16.9 mmol/l D-glucose, it only represented $57.7 \pm 6.7\%$ ($n = 17$; $p < 0.005$) of the mean value found, in the same type of rats, at the low concentration of D-glucose ($100.0 \pm 12.3\%$; $n = 17$). This indicates that the preferential stimulation of oxidative glycolysis at the high hexose concentration coincided with a more efficient oxidation of [1-^{14}C]pyruvate generated from D-[3, 4-^{14}C]glucose and, hence, a lesser fractional conversion of the 2-keto acid to L-[1-^{14}C]alanine.

In sharp contrast to the results obtained for the conversion of D-[3, 4-^{14}C]glucose to either $^{14}CO_2$ or ^{14}C-labelled amino acids, the generation of ^{14}C-labelled acidic metabolites, i.e. mainly L-[1-^{14}C]lactic acid [14], from D-[3, 4-^{14}C]glucose, when expressed relative to the paired production of ^{3}HOH from D-[5-^{3}H]glucose, was higher ($p < 0.001$) in STZ and GK than control rats. Indeed, such paired ratios averaged in the STZ and GK rats, respectively, $162.7 \pm 8.6\%$ ($n = 36$) and $183.2 \pm 17.0\%$ ($n = 26$) of the mean corresponding reference value found in control rats (100.0 ± 6.6; $n = 36$). In absolute terms, the reference value in control rats was higher ($p < 0.02$) at low ($16.1 \pm 2.3\%$; $n = 12$) than high hexose concentration ($9.4 \pm 1.1\%$; $n = 12$) and, in the latter case, tended to be increased in the absence of Ca^{2+} ($12.0 \pm 1.0\%$; $n = 12$). A comparable situation was also observed in both STZ and GK rats.

D-[6-^{14}C]glucose oxidation

The generation of $^{14}CO_2$ from D-[6-^{14}C]glucose is currently used to assess the oxidation in the Krebs cycle of glucose-derived acetyl residues [14].

In control rats, the ratio between D-[6-^{14}C]glucose oxidation and D-[5-^{3}H]glucose utilization was higher at 16.9 than 5.1 mmol/l D-glucose ($p < 0.001$) and, at the high hexose concentration, severely decreased in the absence of Ca^{2+} ($p < 0.001$). Such changes were less marked and failed to achieve statistical significance in islets from STZ rats. Moreover, in the presence of 16.9 mmol/l D-glucose and 1.0 mmol/l Ca^{2+}, the oxidation of D-[6-^{14}C]glucose, expressed relative to the paired generation of ^{3}HOH from D-[5-^{3}H]glucose, was significantly lower ($p < 0.001$) in STZ than control rats.

In the GK rats, as in control animals, the ratio between D-[6-^{14}C]glucose oxidation and D-[5-^{3}H]glucose utilization was increased ($p < 0.001$) as a result of the rise in hexose concentration and, at the high concentration of glucose, decreased ($p < 0.02$) in the absence of Ca^{2+}. However, the absolute values for such a ratio were invariably lower in GK than control rats ($p < 0.02$ or less). Pooling all available data, the ratio averaged in GK rats $68.8 \pm 4.7\%$ ($n = 27$; $p < 0.001$) of the corresponding value found in control animals ($100.0 \pm 1.9\%$; $n = 36$).

Table 3. Unpaired ratio between D-[6-^{14}C]glucose and D-[3, 4-^{14}C]glucose or D-[2-^{14}C]glucose oxidation in islets from control rats, animals injected neonatally with streptozotocin (STZ) and GK rats

Rats (Type)	D-glucose (mmol/l)	Ca^{2+} (mmol/l)	[6-^{14}C]/[3,4-^{14}C]-glucose (%)	[6-^{14}C]/[2-^{14}C]-glucose (%)
Control	5.1	1.0	34.0 ± 2.5	48.1 ± 3.4
	16.9	1.0	34.8 ± 1.4	51.6 ± 2.4
	16.9	Nil	30.6 ± 1.5	43.0 ± 2.9
STZ	5.1	1.0	45.6 ± 4.3	54.1 ± 4.0
	16.9	1.0	38.0 ± 2.9	44.4 ± 2.9
	16.9	Nil	37.6 ± 2.0	53.4 ± 3.1
GK	5.1	1.0	26.5 ± 2.7	31.0 ± 3.8
	16.9	1.0	40.3 ± 3.7	37.2 ± 4.6
	16.9	Nil	27.9 ± 5.4	39.6 ± 7.3

The ratio between D-[6-^{14}C]glucose and D-[3,4-^{14}C]glucose oxidation, both expressed relative to the paired generation of ^{3}HOH from D-[5-^{3}H]glucose, reflects the oxidation of glucose-derived acetyl residues in the Krebs cycle relative to their generation in the reaction catalysed by pyruvate dehydrogenase. Except in GK rats, such a ratio failed to be significantly affected by a rise in D-glucose concentration (Table 3). At the high concentration of D-glucose, it tended to be lower in the absence than presence of Ca^{2+}. Pooling the data collected in the three groups of rats in islets exposed to 16.9 mmol/l D-glucose, the ratio between D-[6-^{14}C]glucose and D-[3,4-^{14}C]glucose oxidation averaged in the absence of Ca^{2+} $86.9 \pm 5.4\%$ ($p < 0.05$) of the mean corresponding value found in the presence of Ca^{2+} ($100.0 \pm 3.9\%$). No obvious impairment of the ratio between D-[6-^{14}C]glucose and D-[3, 4-^{14}C]glucose oxidation was observed in the glucose-intolerant rats. Pooling all available data, such a ratio averaged, in the GK rats, $95.0 \pm 7.5\%$ ($p > 0.5$) of the corresponding value found in control animals ($100.0 \pm 3.2\%$). In the STZ rats, and as judged from data collected in distinct groups of islets, the ratio between D-[6-^{14}C]glucose oxidation and D-[3, 4-^{14}C]glucose oxidation was slightly higher ($121.9 \pm 5.4\%$; $p < 0.001$) than the mean corresponding control value. As shown in Table 3, the overall mean absolute value for the ratio between D-[6-^{14}C]glucose and D-[3, 4-^{14}C]glucose oxidation did not exceed $35.2 \pm 1.1\%$, suggesting that the major fraction of acetyl residues derived from exogenous D-glucose escaped full oxidation in the Krebs cycle.

D-[2-^{14}C]glucose oxidation

In pancreatic islets, the contribution of the pentose phosphate pathway to the oxidation of D-glucose is too low to account for any significant production of $^{14}CO_2$ from D-[2-^{14}C]glucose, as could otherwise result from the recirculation of hexose 6-phosphates in the pentose shunt [15]. Hence, the conversion of D-[2-^{14}C]glucose to $^{14}CO_2$ can be used to assess the oxidation of the C_1 of glucose-derived acetyl residues in the Krebs cycle. It was recently reported

that, in islets, such an oxidation largely exceeds that of the C_2 of the same residues [15].

In the present study, the oxidation of D-[2-^{14}C]glucose was also much higher than that of D-[6-^{14}C]glucose ($p < 0.001$ in all cases). The ratio between D-[6-^{14}C]glucose and D-[2-^{14}C]glucose oxidation, both expressed relative to the paired production of ^{3}HOH from D-[5-^{3}H]glucose, was not vastly different in STZ and control rats, but obviously lower in GK rats. Pooling the data obtained at two D-glucose concentrations and in the absence or presence of Ca^{2+}, such a ratio averaged, in STZ and GK rats respectively, 107.5 ± 4.5 % ($p > 0.19$) and 76.2 ± 7.0 % ($p < 0.005$) of the mean corresponding value found in control rats (100.0 ± 3.6 %).

As already noticed in the case of D-[3, 4-^{14}C]glucose and D-[6-^{14}C]glucose oxidation, the production of $^{14}CO_2$ from D-[2-^{14}C]glucose, when expressed relative to the paired generation of ^{3}HOH from D-[5-^{3}H]glucose, was increased ($p < 0.02$ or less) in response to a rise in hexose concentration and, at the high concentration of D-glucose, decreased in the absence of Ca^{2+} ($p < 0.01$, except in the control rats).

As a rule, the lower oxidation of D-[6-^{14}C]glucose than D-[2-^{14}C]glucose coincided with a higher recovery of ^{14}C-labelled metabolites other than $^{14}CO_2$ with the former compared to the latter tracer. For instance, when expressed relative to the paired generation of ^{3}HOH from D-[5-^{3}H]glucose, the net production of ^{14}C-labelled amino acids from D-[2-^{14}C]glucose averaged 78.7 ± 6.4 % ($n = 97$; $p < 0.005$) of the corresponding mean value found with D-[6-^{14}C]glucose (100.0 ± 3.6 %; $n = 98$) in islets prepared from the same type of rats and incubated within the same experiment under the same experimental conditions.

Discussion

The present results indicate that the rate of glycolysis, as judged from the production of ^{3}HOH from D-[5-^{3}H]glucose, is not significantly different in islets from STZ or GK and control rats, at least when related to the protein content of the islets. This negative finding strongly suggests that any anomaly in hexose transport, leading for instance to a delayed equilibration of D-glucose concentration across the beta-cell plasma membrane, is not sufficient to account for impaired insulin release under near steady-state conditions. It is known from previous studies that glucose-stimulated insulin release is impaired in the islets from STZ and GK rats [16, 17].

Since our metabolic data refer to a mixed population of islet cells as distinct from a pure population of insulin-producing cells, minor differences in the relative contribution of beta cells to the total islet mass could affect selected metabolic variables. However, it should be underlined that the major metabolic phenomenon considered in the present study, namely the Ca^{2+}-dependent preferential stimulation by D-glucose of mitochondrial oxidative events relative to glycolysis, represents an intrinsic characteristic of pure beta cells [18], not observed in purified non-beta islet cells (D. Pipeleers, A. De Vos, F. Schuit and W. J. Malaisse, unpublished observation). Moreover, in the GK rats, the islet insulin content is little affected when related to either the protein or DNA content [17], suggesting a near normal relative contribution of beta cells to the total islet mass.

A reciprocal coupling has been previously documented [12], in islets from normal rats, between mitochondrial oxidative events and ATP-requiring and glucose-responsive functional processes such as active Ca^{2+} pumping and insulin release. It could be argued that an impairment of the former events may be, at least in part, secondary to the secretory defect. In the present study, however, well-defined anomalies in the ratio between D-glucose oxidation and utilization were also documented in islets incubated in the absence of extracellular Ca^{2+}.

The present findings do not rule out subtle anomalies in the overall glycolytic response of islet cells to a rise in D-glucose concentration. The ratio in glycolytic flux from 16.9 mmol/l to 5.1 mmol/l D-glucose was indeed significantly lower in STZ and GK than control rats. However, this anomaly could be the consequence of an impaired stimulation of oxidative glycolysis in the diabetic animals.

In both STZ and GK rats, the ratio between D-[3, 4-^{14}C]glucose oxidation and D-[5-^{3}H]glucose conversion to ^{3}HOH was about 25 % lower than in control rats. This suggests a preferential deficiency of the oxidative modality of glycolysis, which is coupled with the transfer of reducing equivalents into the mitochondria, as mediated for instance by the glycerol phosphate shuttle [19] and, hence, not associated with the generation of L-lactate. It has previously been shown that, in STZ rats, this preferential impairment of oxidative glycolysis coincides with a decreased flow through the glycerol phosphate shuttle [20, 21].

In pancreatic islets, the net generation of ^{14}C-labelled pyruvate and L-alanine from D-[3, 4-^{14}C]glucose is much lower than its oxidation rate [22]. The present study further indicates that, relative to D-[5-^{3}H]glucose utilization, the production of ^{14}C-labelled L-alanine from D-[3, 4-^{14}C]glucose was significantly lower in STZ or GK than control rats. These findings strongly suggest that the low ratio between D-[3, 4-^{14}C]glucose oxidation and D-[5-^{3}H]glucose utilization found in diabetic animals reflects an altered ratio between oxidative and total glycolysis, rather than a primary defect in the activity of pyruvate dehydrogenase. Thus, if the velocity of the reaction catalysed by pyruvate dehydrogenase were to be decreased, without any perturbation in the ratio between oxidative and total glycolysis, an excessive amount of ^{14}C-labelled pyruvate and L-alanine would be expected to be generated from D-[3, 4-^{14}C]glucose.

As judged from the ratio between D-[6-^{14}C]glucose and D-[3, 4-^{14}C]glucose, the oxidation of acetyl residues in the Krebs cycle, relative to their generation in the reaction catalysed by pyruvate dehydrogenase, was also not impaired in diabetic animals. The absence of any major primary metabolic defect in the Krebs cycle of STZ or GK rats is further supported by the finding that the unpaired ratio between D-[2-^{14}C]glucose and D-[3, 4-^{14}C]glucose oxidation was slightly higher in diabetic than control rats. Pooling all available data, such a ratio averaged in STZ and GK rats, respectively, 115.0 ± 6.0 and 126.9 ± 10.1 %

($p < 0.05$ or less) of the corresponding value found in control rats ($100.0 \pm 3.9\%$). The lower ratio between D-[6-^{14}C]glucose and D-[2-^{14}C]glucose oxidation in the GK rats would then suggest that the influx into the Krebs cycle of 4- or 5-carbon metabolites derived from endogenous unlabelled nutrients is higher, relative to the inflow into the same cycle of acetyl residues, in GK than either control or STZ rats [15].

In conclusion, the present study suggests that in GK as well as in STZ rats, the impaired insulin secretory response to D-glucose might be caused, at least in part, by an altered ratio between oxidative and total glycolytic flux. In the STZ rats, this metabolic anomaly was attributed to a site-specific defect in the activity of the mitochondrial FAD-linked glycerophosphate dehydrogenase [11, 20]. Further studies, in progress, are required to document whether a comparable enzymatic defect is present in the islets of GK rats. Meanwhile, our findings reveal that a preferential perturbation of oxidative glycolysis in pancreatic islets represents a metabolic feature of non-insulin-dependent diabetes not only in adult rats injected with streptozotocin during the neonatal period (STZ rats) but also in diabetic GK rats obtained by selective breeding over numerous generations [3, 4]. Therefore, the preferential perturbation of oxidative glycolysis could conceivably represent a mechanism leading to spontaneous, as distinct from drug-induced, non-insulin-dependent diabetes.

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