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*Originals*

# Normal insulin sensitivity during the phase of glucose intolerance but insulin resistance at the onset of diabetes in the spontaneously diabetic BB rat

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**Summary.** In diabetes-prone BB rats, 30 to 50% of animals undergo autoimmune destruction of the pancreatic B-cells leading to a short period of glucose intolerance, followed by an abrupt onset of diabetes. We have examined whether the glucose intolerance period and the onset of diabetes are associated with changes in insulin sensitivity, using the euglycaemic hyperinsulinaemic clamp coupled with [3-$^3$H] glucose infusion. Glucose intolerant rats were detected by a transient glycosuria one hour after an oral glucose load performed every four days. Insulin sensitivity studied in these rats the day following their detection was normal. Other diabetes-prone BB rats were tested daily and studied on the first day of glycosuria. In the basal state, glucose production was increased in diabetic rats ($11.3 \pm 1.1$ vs $7.1 \pm 0.8$ mg·min$^{-1}$·kg$^{-1}$, $p < 0.05$). Tissue glucose utilization was similar in diabetic and control rats ($8.3 \pm 0.5$ vs $7.1 \pm 0.8$ mg·min$^{-1}$·kg$^{-1}$) despite a three fold higher glycaemia in the diabetic rats. During the hyperinsulinaemic clamps, glycaemia was clamped at 6.1-6.6 mmol/l in diabetic and control rats. A decreased insulin sensitivity was observed in diabetic rats at submaximal (200 μU/ml) and maximal (1500 μU/ml) insulin concentrations for both inhibition of hepatic glucose production and stimulation of glucose utilization. No autoantibodies against insulin could be detected in the plasma of diabetic rats. Plasma concentrations of glucagon, catecholamines, ketone bodies and fatty acids were similar in control and diabetic rats during the clamp studies. Our results suggest that the decrease of basal insulin concentration is responsible for the insulin resistance in the diabetic BB rat at onset of diabetes, either directly or through the increased glycaemia.

**Key words:** BB rat, diabetes, glucose intolerance, insulin sensitivity.

Insulin resistance has been largely reported in Type 1 (insulin-dependent) diabetes mellitus, both in newly-diagnosed and in long-standing diabetic patients who have received exogenous insulin therapy [1, 2]. Long-standing diabetic patients have been exposed to hyperinsulinaemia due to conventional insulin therapy and to long-term metabolic disturbances, both factors which are known to induce a state of insulin resistance [3, 4]. By contrast, newly-diagnosed diabetic patients have been exposed for various time periods to a state of hypoinsulinaemia and its secondary metabolic consequences (hyperglycaemia, hyperlipaemia, hyperketonaemia). The relative roles of insulin lack and that of metabolic disturbances involved in insulin resistance at the onset of Type 1 diabetes in human subjects, are not known. The spontaneously diabetic BB rat described by Nakhooda and Marliss [5, 6] closely approximates human Type 1 diabetes. In this model, between 60 and 120 days of age, 30 to 50% of susceptible animals undergo cell-mediated and humoral autoimmune destruction of B-cells and a decreased insulin secretion. Decreasing insulin secretory capacity induces a period of glucose intolerance without basal metabolic disturbances until an abrupt onset of hyperglycaemia with glycosuria [7-9]. The BB rat model, therefore, provides a means to examine whether variations of insulin sensitivity coexist with the relative insulin deficiency during glucose intolerance or with the acute insulinopoenia on the first day of glycosuria, when the diabetic rat has suffered from metabolic disturbances for a very short period of time.

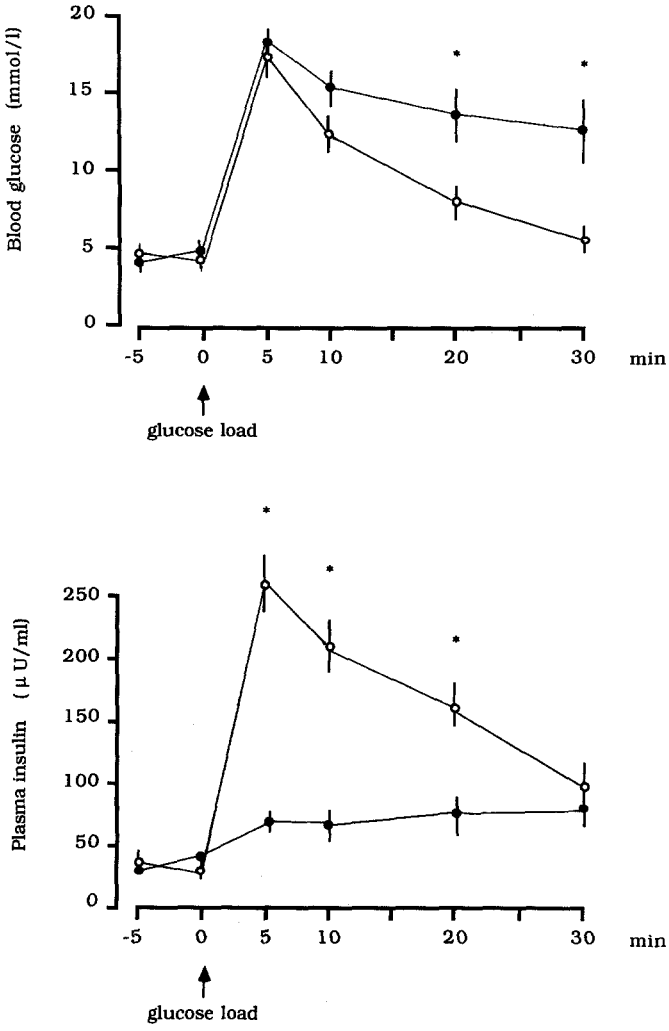


**Fig. 1.** Blood glucose and plasma insulin concentrations in eight glucose intolerant (●) and eight control (○) rats during i.v. glucose tolerance tests (1 mg/g body weight). Results are means ± SEM. * Difference significant for $p < 0.001$ when compared with the control group

## Materials and methods

### *Animals*

The BB rats were obtained from Dr. P. Thibert (Animal Resources Division, Health protection branch, Ottawa, Canada).

These animals were the offspring of matings between an insulin-treated diabetic male and a non-diabetic female known to have produced previous diabetic progeny. The results of all studies were compared with those of age and sex-matched control rats obtained from the same strain but from breeding pairs which have never produced diabetic offspring in a minimum of five sequential litters. Animals were housed in individual cages, fed chow pellets (24% protein, 4% fat, 57% carbohydrate, 6% cellulose, 9% minerals, weight/weight) ad libitum, and weighed daily. Temperature, humidity and lighting were strictly controlled.

### *Time course of metabolic and hormonal disturbances during development of diabetes in BB rats*

In an attempt to characterize the time course of metabolic and/or hormonal disturbances during the development of diabetes, 43 diabetes-prone BB rats, at 70 days of age, were anaesthetised with ether and operated on under clean, but non-sterile, conditions. A bevel-edged silastic catheter (Silastic 602-105, Dow Corning Co, Midland, Mich, USA) was inserted into the jugular vein and pushed to the right atrium of the heart. The catheter was driven subcutaneously to the top of the skull, fixed with cement (Texton, SS White, Paris, France) and occluded with a metal plug following a flush of heparinized 0.9% NaCl solution. After recovery of the preoperative body weight (usually, three days), the long-term intracardiac catheter allowed daily blood sampling (150 μl) to be performed between 09.00 hours and 10.00 hours in conscious rats in the resting state, for the determination of basal blood glucose, ketone body and plasma insulin concentrations until the first day of glycosuria.

### *Detection of glucose intolerance in the BB rats*

In a preliminary study, in order to set up a simple and reliable test to detect glucose intolerant rats, an oral glucose tolerance test (OGTT, 3.5 mg/g body weight) was performed in 20 diabetes-prone BB rats and urine was tested for glucose one h later. The test was repeated every four days and allowed to detect eight rats with a transient glycosuria. These eight rats were anaesthetised the following day with pentobarbital (30 mg/kg body weight, i.p.) and underwent an i.v. glucose load (1 mg/g body weight). Eight rats from the same litters which were negative for urinary glucose after the OGTT were used as control animals. Blood was sampled at 5, 10, 20 and 30 min after the load, for plasma insulin determination (RIA insulin kit, ORIS Industrie SA, Gif/Yvette, France) and blood glucose measurement (glucose oxidase kit, Boehringer, Mannheim, FRG) after blood deproteinization with 5 volumes of $HCILO_4$ (6%, weight/volume), centrifugation (16000 *g*, 2 min) and neutralization. The results are presented in Figure 1. All the BB rats transiently glycosuric after the OGTT showed a marked glucose intolerance and a decreased insulin secretory capacity when compared to control rats negative for glycosuria (at 5 min, the highest insulin value in the former group was 92 μU/ml, whereas the lowest value in the latter was 190 μU/ml). Using this method, we tested 33 diabetes-prone BB rats every four days.

### *Detection of diabetic BB rats*

Fifty additional BB rats were monitored daily for body weight and glycosuria at 08.00 hours. These animals later made up the diabetic rat group on their first day of glycosuria.

### *Glucose turnover rate in the basal state in diabetic rats*

On the first day of glycosuria, at 14.00 hours, and following a 6 h fast, six diabetic rats and the sex and age-matched control rats were anaesthetised with pentobarbital (30 mg/kg body weight i.p.); a tracheotomy was performed and a carotid artery catheterised. The bladder of the diabetic rats was catheterised and emptied. Body temperature was continuously recorded with a telethermometer and carefully maintained at 38 °C with heating lamps and pads. A tracer dose of [3-$^3$H] glucose (15 μCi [Amersham, Bucks, UK]) in 300 μl of heparinized (100 IU/ml) 0.9% NaCl was injected as a bolus through a saphenous vein and arterial blood aliquots were sampled at 1, 3, 5, 10, 20 and then, every 20 min until 160 min after the injection.

Blood samples (50 μl) were deproteinised with 250 μl $ZnSO_4$ (2.71%) and 250 μl of $Ba(OH)_2$ (2.62%) and immediately centrifuged. An aliquot of the supernatant was used for the determination of glucose concentration and another aliquot was evaporated to dryness to remove tritiated water and redissolved in water before counting the radioactivity in a scintillation spectrometer (B-matic, Kontron, France). At the time 160 min, the bladder of the diabetic rats was emptied and an aliquot of urine was treated in the same manner as blood samples for the determination of the amount of [3-$^3$H] glucose. At time 160 min, the specific activity of blood glucose was less than 2% of the 1 min value. The glucose turnover rate (Rg) was calculated as follows:

$$\text{Rg (mg/min)} = \frac{\text{[3-}^3\text{H] glucose injected (dpm)}}{\int_0^{160\text{ min}} \text{blood glucose specific activity (dpm/mg)}}$$

The rate of urinary glucose excretion (Ru) was calculated as follows:

$$\text{Ru (mg/min)} = \frac{\text{total urinary [3-}^3\text{H] glucose (dpm)}}{\int_0^{160\text{ min}} \text{blood glucose specific activity (dpm/mg)}}$$

The rate of glucose utilization by tissues (mg/min) was

glucose turnover rate (mg/min) − urinary glucose excretion (mg/min).

### *Euglycaemic hyperinsulinaemic clamps in glucose intolerant and diabetic rats*

Using the euglycaemic hyperinsulinaemic clamp technique, insulin sensitivity was studied in eight glucose intolerant rats on the day following the detection of intolerance by OGTT and in 19 diabetic rats on the first day of glycosuria. At 14.00 hours, following a 6 h fast, animals were anaesthetised and operated on as described previously for the determination of the glucose turnover rate. Euglycaemic hyperinsulinaemic clamps were thus performed in the post-absorptive state [10] as previously described [11]. Briefly, a variable glucose infusion and a constant insulin infusion (Crystalline pork insulin, Novo Industry, Copenhagen, Denmark) were delivered through saphenous veins. In glucose intolerant and control rats, an insulin perfusion rate of $0.4\ \text{U}\cdot\text{h}^{-1}\cdot\text{kg}^{-1}$ was used. In diabetic rats and the control animals, two rates of insulin perfusion were used in two different series of experiments: $0.4\ \text{U}\cdot\text{h}^{-1}\cdot\text{kg}^{-1}$ (clamp A) and $1.6\ \text{U}\cdot\text{h}^{-1}\cdot\text{kg}^{-1}$ (clamp B). Blood glucose concentration was measured every 5 min on 20 µl samples using a glucose analyser (YSI, 23A, Yellow Springs Instrument Co., Yellow Springs, Ohio, USA). Adjustments of the glucose perfusion rate were made to maintain euglycaemia. In diabetic rats, to avoid urinary glucose excretion and to perform the clamps in similar glycaemic and insulinaemic conditions as in control rats, the blood glucose concentration was first allowed to decrease to about 6.1-6.6 mmol/l and was then maintained at this concentration with variable glucose infusion. A steady-state for both glycaemia and exogenous glucose infusion rate was obtained in 40 min in both control and glucose intolerant rats and in 60 min for the diabetic rats. The rate of glucose utilization was determined by a primed continuous infusion of [3-$^3$H] glucose added to the insulin infusion medium. The priming dose was 20 µCi/kg and the perfusion rate was $1\ \mu\text{Ci}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$. Hepatic glucose production was calculated from the difference between the rate of glucose utilization and the rate of exogenous glucose infusion.

Blood samples (50 µl) were collected at 20, 27 and 35 min after the achievement of the steady state, for the determination of blood glucose specific activity. Blood samples (500 µl) were collected before insulin infusion and at the end of the experiment for the determination of non-esterified fatty acids (NEFA C enzymic kit, Biolyon, Dardilly, France), ketone body [12], insulin, pancreatic glucagon (glucagon kit, Serono Diagnostic SA, Coinsins, Switzerland), epinephrine and norepinephrine [13], autoantibodies against insulin [14] and $HbA_{1c}$ (Merckotest Glyc-Hb, Darmstadt, FRG).

### *Statistical analysis*

Results are presented as means ± SEM. Statistical significance of differences was assessed by the Student's *t*-test.

## Results

### *Glucose intolerant rats*

*Incidence.* Among 33 diabetes-prone BB rats, 15 were found to be glucose intolerant (i.e.; incidence = 45%). The day after detection of their glucose intolerance, seven rats were diabetic, and the eight remaining glucose intolerant rats had normal basal glycaemia. These eight latter rats and six control rats negative for glycosuria after OGTT were tested by the euglycaemic hyperinsulinaemic clamp technique.

**Table 1.** Circulating substrate and hormone concentrations, and glucose kinetics in the basal state and during euglycaemic hyperinsulinaemic clamp in postabsorptive anaesthetised control and glucose intolerant rats. Results are means ± SEM with the number of determinations *(n)*

| | Basal state | | Clamp (150 µU/ml) | |
|---|---|---|---|---|
| | Control rats ($n=6$) | Glucose intolerant rats ($n=8$) | Control rats ($n=6$) | Glucose intolerant rats ($n=8$) |
| Glucose (mmol/l) | 4.7 ± 0.2 | 5.3 ± 0.2 | 4.9 ± 0.2 | 5.1 ± 0.1 |
| B-hydroxybutyrate (mmol/l) | 0.20 ± 0.04 | 0.24 ± 0.10 | 0.08 ± 0.06 | 0.06 ± 0.07 |
| NEFA (mmol/l) | 0.47 ± 0.06 | 0.39 ± 0.07 | 0.31 ± 0.05 | 0.22 ± 0.03 |
| Insulin (µU/ml) | 38 ± 6 | 42 ± 4 | 156 ± 6 | 140 ± 8 |
| Glucose utilization ($\text{mg}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$) | - | - | 15.6 ± 0.8 | 16.6 ± 1.1 |
| Glucose production ($\text{mg}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$) | - | - | 0.4 ± 0.4 | 1 ± 0.4 |

NEFA: non-esterified fatty acids. There was no statistically significant difference between control and glucose intolerant rats whatever the parameter studied

*Insulin sensitivity.* The concentrations of substrates and hormones in anaesthetised glucose intolerant rats in the basal state are shown in Table 1. Blood glucose and ketone body concentrations, as well as plasma NEFA and insulin concentrations were similar in the two groups. $HbA_{1c}$ was also identical in control (3.9 ± 0.2%, $n=6$) and glucose-intolerant rats (4.1 ± 0.4%, $n=8$). During the clamp studies and for hyperinsulinaemia of 150 µU/ml, ketone body and NEFA concentrations showed a similar decrease in the two groups.

Moreover, in the glucose-intolerant rats, glucose production was inhibited and glucose utilization was stimulated to the same extent as in the control animals (Table 1).

### *Diabetic rats*

*Incidence and time-course of diabetes.* Long-term catheterization in 43 diabetes-prone BB rats allowed us to compare in conscious resting animals the concentration of various circulating substrates and of insulin in control rats and in rats one day before the onset of diabetes. In the future diabetic rats, blood ketone body, plasma NEFA and insulin concentrations remained within the normal range until the detection of glycosuria (Table 2). In some rats, basal blood glucose concentrations were

**Table 2.** Circulating substrate and insulin concentrations in postabsorptive control and diabetic rats one day before glycosuria. Blood was sampled in conscious catheterized animals. Results are means ± SEM with the number of determinations *(n)*

| | Control rats ($n=5$) | Future diabetic rats one day before glycosuria ($n=5$) |
|---|---|---|
| Glucose (mmol/l) | 6.1 ± 0.3 | 7.2 ± 1 |
| B-hydroxybutyrate (mmol/l) | 0.27 ± 0.05 | 0.24 ± 0.06 |
| NEFA (mmol/l) | 0.50 ± 0.04 | 0.48 ± 0.05 |
| Insulin (μU/ml) | 30 ± 4 | 32 ± 5 |

NEFA: Non-esterified fatty acids. There was no significant statistical difference between control and future diabetic rats whatever the parameter studied

higher than normal one day before the major increase leading to glycosuria (Table 2). The incidence of diabetes among the 93 high risk BB rats was 27%. The age at onset varied from 65 to 120 days with a mean at 91 ± 4 days.

*Diabetic rats in the basal state.* The concentrations of substrates and hormones in anaesthetised diabetic rats on the first day of glycosuria and in control rats are shown in Table 3. Blood glucose and ketone body concentrations were respectively three and two fold higher in the diabetic than in the control rats. Plasma NEFA concentrations in diabetic rats were the same.

Plasma glucagon, epinephrine and norepinephrine concentrations were similar in the two groups (Table 3), whereas insulin concentration was lower in diabetic than in control rats. Autoantibodies against insulin which are commonly found in the sera of Type 1 diabetic patients, were undetectable in the diabetic and in the control rats. $HbA_{1c}$ was slightly but significantly higher in the diabetic than in the control rats (5.5 ± 0.3%, $n=10$ vs 4.3 ± 0.2%, $n=7$, $p<0.01$).

In the basal state, glucose production was increased (+60%) in diabetic rats (11.3 ± 1.1 vs 7.1 ± 0.8 mg · $min^{-1} \cdot kg^{-1}$, $n=6$, $p<0.05$). However, when the urinary glucose excretion was taken into account, there was no significant difference in the rate of tissue glucose utilization in diabetic and control rats (8.3 ± 0.5 vs 7.1 ± 0.8 mg · $min^{-1} \cdot kg^{-1}$, $n=6$).

*Insulin sensitivity.* Insulin sensitivity was assessed by the euglycaemic hyperinsulinaemic clamp at similar blood glucose and plasma insulin concentrations in diabetic and control rats. The two rates of glucose infusion used (clamp A: 0.4 U · $h^{-1} \cdot kg^{-1}$ and clamp B: 1.6 U · $h^{-1} \cdot kg^{-1}$) allowed to reach steady-state plasma insulin concentrations (SSPI) similar in diabetic and control rats (clamp A: 200 μU/ml; clamp B: 1480 μU/ml). Substrate and hormone concentrations during clamp A and B are shown in Table 3. Ketone body concentrations, which were greater in diabetic than in control rats in the basal state were decreased during clamp B and became similar to those of control rats. Plasma NEFA concentrations were slightly decreased during the clamp but remained identical in the two groups.

Despite the decrease in glycaemia induced by insulin in diabetic rats, none of the counterregulatory hormones tested (glucagon, epinephrine, norepinephrine) were increased during the euglycaemic clamp when compared to the basal state.

Glucose utilization and production are presented in Figure 2. For both insulin concentrations 200 μU/ml (clamp A) and 1480 μU/ml (clamp B), glucose utilization was significantly lower (−30%) in diabetic than in control rats. Hepatic glucose production was totally suppressed in control rats whereas it was suppressed by only 50% in diabetic rats.

In three diabetic rats, it was not possible to normalise blood glucose concentration (13.7, 16 and 18.7 mmol/l) during the clamp despite the presence of high plasma insulin concentrations (respectively 356, 250 and 234 μU/ml). These three values are not included in the means presented in Figure 2.

## Discussion

In human Type 1 diabetes, insulin action is altered both in newly-diagnosed [1, 15] or long-standing diabetes [2, 16–18] but the mechanism of the development of this

**Table 3.** Circulating substrate and hormone concentrations in the basal state and during euglycaemic hyperinsulinaemic clamp in postabsorptive anaesthetised control and diabetic rats on first day of glycosuria. Results are means ± SEM with the number of determinations *(n)*

| | Basal state | | Clamp (200 μU/ml) | | Clamp (1480 μU/ml) | |
|---|---|---|---|---|---|---|
| | Control rats ($n=25$) | Diabetic rats ($n=25$) | Control rats ($n=10$) | Diabetic rats ($n=10$) | Control rats ($n=9$) | Diabetic rats ($n=9$) |
| Glucose (mmol/l) | 5.8 ± 0.4[c] | 17.2 ± 1.3 | 6 ± 0.3 | 6 ± 0.3 | 6.2 ± 0.3 | 6.7 ± 0.4 |
| B-hydroxybutyrate (mmol/l) | 0.21 ± 0.03[b] | 0.49 ± 0.08 | ND | ND | 0.17 ± 0.05 | 0.17 ± 0.07 |
| NEFA (mmol/l) | 0.47 ± 0.04 | 0.50 ± 0.05 | 0.25 ± 0.01 | 0.27 ± 0.02 | 0.32 ± 0.03 | 0.33 ± 0.04 |
| Insulin (μU/ml) | 35 ± 3[b] | 20 ± 3 | 200 ± 27 | 219 ± 30 | 1479 ± 172 | 1485 ± 290 |
| Glucagon (pg/ml) | 261 ± 26 | 275 ± 32 | 177 ± 26 | 230 ± 62 | 246 ± 27 | 216 ± 31 |
| Epinephrine (pg/ml)[a] | 761 ± 22 | 881 ± 143 | 898 ± 85 | 988 ± 121 | ND | ND |
| Norepinephrine (pg/ml)[a] | 930 ± 99 | 1121 ± 172 | 941 ± 57 | 1335 ± 145 | ND | ND |

[a] Epinephrine and norepinephrine concentrations in basal state were determined for $n=10$. [b] $p<0.05$ and [c] $p<0.001$ compared with the control group. NEFA: non-esterified fatty acids; ND: not determined

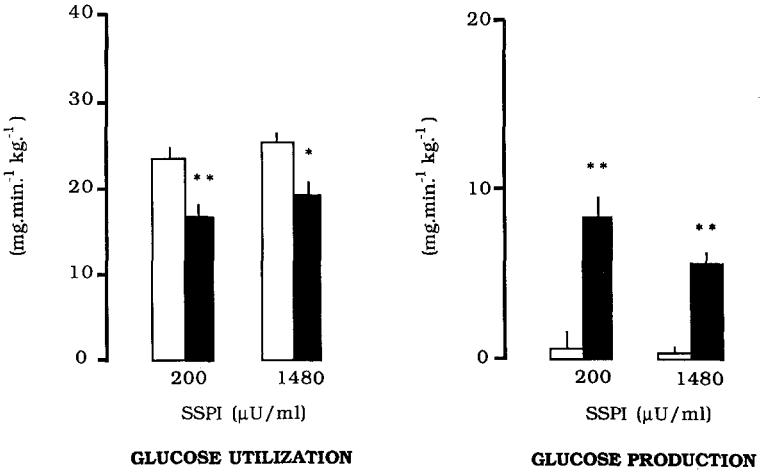


**Fig. 2.** Glucose utilization and production during the euglycaemic hyperinsulinaemic clamp studies in post-absorptive anaesthetised control (□) and diabetic (■) rats. SSPI: steady state plasma insulin concentrations. The corresponding glycaemia is indicated in Table 3. Results are means ± SEM. Differences significant for * $p < 0.05$ and ** $p < 0.001$ when compared with the control group

insulin resistance is poorly understood. The BB rat model, in which the time course of metabolic and hormonal environment can be accurately characterized is appropriate to determine the time-course of insulin resistance during the development of diabetes.

In an attempt to follow the appearance of metabolic and hormonal disturbances, diabetes-prone animals have been catheterized on a long-term basis. The surgery, the presence of intracardiac catheter and the daily blood sampling did not induce infection in the BB rats despite their altered immunity [19] and allowed blood sampling without stress or anaesthesia. It confirmed [7] that none of the measured criteria in the post-absorptive state (NEFA, ketone bodies, insulin and glucose concentrations) can be used as a reliable marker of the prediabetic period. Previous studies [7, 8, 20] and the present work have shown that in spite of this normal metabolic situation in the post-absorptive state, an inadequate insulin secretion in response to glucose appears 1–2 weeks before the onset of diabetes. This implies that the normal meal-induced insulin excursions do not take place during this period. Other physiological situations with continuously low insulin concentrations such as fasting [21] or suckling [22] are accompanied by insulin resistance. The absence of insulin resistance in glucose-intolerant BB rats suggests that a normal insulin concentration in the post-absorptive range is sufficient to maintain a normal insulin sensitivity.

Diabetes in BB rats is characterized on the first day of glycosuria by an increased basal hepatic glucose production which is the consequence of both hypoinsulinaemia and hepatic insulin resistance as shown by the clamp studies. In contrast, in human Type 1 diabetic subjects, a normal insulin suppression of hepatic glucose production was found after a 24 h withdrawal of the insulin treatment [16]. This experimental condition might have dampened the consequence of insulin deficiency on hepatic insulin sensitivity.

On the first day of glycosuria, a normal basal rate of glucose utilization was achieved in diabetic BB rats in the presence of marked hyperglycaemia, known to increase glucose utilization by a mass-action effect. Normalisation of blood glucose concentration during the clamp studies shows insulin resistance of glucose utilization in the diabetic BB rats.

What are the possible causes of this hepatic and peripheral insulin resistance?

During the euglycaemic clamp, plasma glucagon, epinephrine and norepinephrine concentrations in diabetic rats with normalised glycaemia were similar to those found in control rats. This suggests that counter-regulatory hormones are probably not involved in the hepatic and peripheral insulin resistance observed in diabetic BB rats.

Elevated concentrations of plasma NEFA and blood ketone bodies are known to reduce insulin-mediated glucose uptake especially in muscles [23]. Although blood ketone body concentrations were elevated in the basal state in diabetic rats, they reached similar levels in diabetic and control rats during the euglycaemic clamp. Moreover, hyperinsulinaemia decreased plasma NEFA to the same extent in the two groups during the clamp. This suggests that NEFA and ketone bodies could not inhibit glucose utilization in diabetic rats and that the antilipolytic effect of insulin is not altered in diabetic BB rats.

Insulin resistance could be the consequence of the presence of autoantibodies against insulin. Indeed, insulin autoantibodies are found in 20 to 50% of newly-diagnosed untreated Type 1 diabetic subjects [24, 25]. Wilkin et al. [26] have found a higher insulin binding capacity in the plasma of diabetes-prone rats when compared to control rats, whereas Dean et al. [27] have found only a weak association between the presence of autoantibodies against insulin and the development of diabetes in BB rats. In accordance with the present study, other authors [28] have found no detectable autoantibodies, strongly suggesting that immunological factors do not counteract insulin action in the diabetic BB rats at the onset of diabetes.

Hyperglycaemia per se has also been involved in the development of insulin resistance [3]. Indeed, an insulin

resistant state observed in partially pancreatectomized rats was overcome by correcting the hyperglycaemia with phlorizin [29]. In the glucose intolerant rats, the normal percentage of $HbA_{1c}$ suggests that episodes of meal-induced hyperglycaemia remained very mild. In contrast, on the first day of glycosuria $HbA_{1c}$ was slightly but significantly increased in the diabetic rats ($p < 0.01$). Thus, one cannot exclude a possible role of hyperglycaemia in the development of insulin resistance in diabetic rats.

In summary, in BB rats, insulin sensitivity is normal during the impaired glucose tolerance period preceding diabetes, but a hepatic and peripheral insulin resistance appears at the onset of diabetes. It is then tempting to speculate that the decrease of basal insulin concentration observed during this transition is responsible for the insulin resistance in the diabetic BB rats at the onset of diabetes either directly or through the increased glycaemia.

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