Increased Epinephrine-Induced cAMP Response in Severely Diabetic BB/W Rat Liver

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Abstract. The effect of prolonged diabetes on epinephrine-induced adenosine 3',5'-monophosphate (cAMP) response in the liver was examined in diabetes-prone BB/W rats. Basal and 1 μM epinephrine-induced cAMP release from isolated perfused liver was similar in non-diabetic and diabetic BB/W rats with preserved adipose tissue. In adipose tissue-absent diabetic rats losing intra- and retro-peritoneal adipose tissue completely, both basal and 1 μM epinephrine-induced cAMP release from the liver were enhanced (P<0.01, each case). Plasma epinephrine and norepinephrine were similar in non-diabetic, adipose tissue-preserved and -absent diabetic BB/W rats. The plasma free thyroxine level was similar in non-diabetic and adipose tissue-preserved diabetic BB/W rats, but was lower in adipose tissue-absent diabetic BB/W rats than in non-diabetic rats (P<0.01), but the frequency of lymphocytic thyroiditis was similar in these three groups, although plasma corticosterone was lower in adipose tissue-preserved diabetic BB/W rats (P<0.05) and the lowest in adipose tissue-absent diabetic BB/W rats (P<0.01). Lymphocytic infiltration was not observed in the adrenal or pituitary glands in any group. Plasma total protein and albumin were low in adipose tissue-absent diabetic BB/W rats (P<0.01, each case). In adipose tissue-absent diabetic BB/W rats, liver dysfunction and hepatomegaly, but no apparent histological change in the liver, were observed. Plasma glucose was higher (P<0.01) and plasma insulin lower (P<0.05) in adipose tissue-absent diabetic BB/W rats than in adipose tissue-preserved diabetic BB/W rats. In conclusion, epinephrine-induced cAMP response in the liver was enhanced only in adipose tissue-absent diabetic BB/W rats. Denervation supersensitivity was not likely to be responsible for the enhanced β-adrenergic response. The observed reductions in plasma thyroxine and corticosterone seemed to result from severe diabetes. Although the severity of diabetes can vary continuously, severe diabetes with loss of adipose tissue appeared to cause significant changes in the metabolism and enhanced β-adrenergic response in the liver.

Key words: BB/W rat, Liver dysfunction, Adenosine 3',5'-monophosphate (cAMP), Epinephrine, Adipose tissue

HEPATIC glucose overproduction is a common feature of diabetes mellitus [1, 2]. The intracellular adenosine 3',5'-monophosphate (cAMP) level regulates not only the activity of key enzymes of glucose metabolism in hepatocytes, but also enzyme gene expression [3]. It is therefore important to determine the activity of adenyll cyclase in diabetic liver. Classically, hormone-induced cAMP production is thought to be enhanced in the diabetic liver, since insulin suppresses the cAMP level [4]. Metabolic and cardiovascular responses to epinephrine are
increased in diabetics with autonomic neuropathy [5], but conflicting results concerning the activity of epinephrine-responsive adenylyl cyclase have been reported for streptozotocin-induced diabetic rat liver [6–8].

We recently found that epinephrine- and isoproterenol-induced cAMP production was markedly enhanced in the liver of extremely emaciated diabetic rats without adipose tissue, but not in the liver of diabetic rats with preserved adipose tissue, 4 weeks after streptozotocin-injection and kept without insulin [9]. But liver dysfunction was observed when streptozotocin-injected rats were kept without insulin, as reported by Lauguens et al. [10]. Enhanced β-adrenergic response has been reported in partially hepatectomized [11] and cholestatic [12] rat hepatocytes. In these circumstances, deterioration of liver function occurs. Liver dysfunction may therefore be responsible for increased cAMP production in streptozotocin-induced diabetic rat liver.

In the present study, to avoid streptozotocin-induced liver damage, we used genetically diabetic BB/W rats [13] to examine epinephrine-induced cAMP production in diabetic rat liver, and attempted to determine whether loss of adipose tissue is required for enhanced β-adrenergic response in the liver. Increased β-adrenergic response in rat liver has been reported in hypothyroid [14, 15], adrenalectomized [16, 17] and hypothalamic-lesioned [18] conditions as well. Because BB/W rats are known to suffer from lymphocytic thyroiditis in addition to insulitis [13, 19], we also examined hormone levels and performed histological studies on BB/W rats.

Materials and Methods

Animals

BB/W rats were kindly provided by the Animal Research Center, Tokyo Medical College [19], and maintained at the Laboratory Animal Center, Yamagata University School of Medicine. The rats were fed ad libitum on a standard rat chow (Nippon Charles River, Atsugi, Japan) and kept without insulin. A total of 112 male BB/W rats were used for the experiments. Urinary glucose was checked with test paper (Diastix, Miles-Sankyo, Tokyo, Japan) once a week. Rats testing negative for urinary glucose were considered non-diabetic (n=35), and those testing positive were considered diabetic (n=77). Diabetic BB/W rats were divided by chance into two groups, adipose tissue-present and -absent at the time of abdominal incision (n=39 and 38, respectively). Although the amount of adipose tissue varied continuously, it was easy to distinguish between adipose tissue-present and -absent diabetic rats. Adipose tissue-absent diabetic rats losing intra- and retro-peritoneal adipose tissue completely were negative on urine ketone testing (Ketostix, Miles-Sankyo, Tokyo, Japan). The duration of diabetes was estimated to be one to three weeks based on positive urinary glucose tests. Normal male Wistar rats were used as normal controls (n=25).

Liver perfusion

Rats were used in the fed ad libitum state, and anesthetized with 60 mg/kg intraperitoneal injection of pentobarbital. After incision of the abdominal wall, blood was collected from the inferior vena cava into tubes containing EDTA-2Na (final concentration, 1 mM) and aprotonin (500 KIU/ml, Bayer, Leverkusen, Germany), and then the liver was isolated. The plasma was quickly isolated, and stored at −20 °C. The isolated liver was perfused noncyclically at a rate of 30 ml/min through the portal vein at 32 °C [20, 21]. The perfusion medium was a hemoglobin-free solution of 115 mM NaCl, 5.9 mM KC1,1.2 mM MgCl2,1.2 mM NaH2PO4,1.2 mM Na2SO4, 2.5 mM CaCl2 and 25 mM NaHCO3, pH 7.4, aerated with a mixture of 95% O2 and 5% CO2 throughout the experiment. After a control period of 30 min, 1 μM epinephrine (final concentration, Daiichi Pharmaceutical, Tokyo, Japan) was infused through a side arm. The effluent was collected from the inferior vena cava at 1-min intervals.

Histology

The pancreas, liver, thyroid gland and adrenal gland were excised from different series of BB/W rats and fixed in 10% formalin, embedded in paraffin and cut into 4-μm-thick sections. These sections were stained by a routine hematoxylin &
eosin method. PAS staining was performed for the liver sections.

Assays

Glucose was measured by glucose oxidase methods (Boehringer-Mannheim-Yamanouchi, Tokyo, Japan, for the effluent from the perfused liver, and Wako, Osaka, Japan, for the plasma). Glucagon (Otsuka Assay Laboratory, Tokushima, Japan), free thyroxine (Japan Kodak Diagnostics, Tokyo, Japan) and cAMP (Yamasa Shoyu, Choshi, Japan) were assayed with commercially available radioimmunoassay kits. Insulin was assayed by radioimmunoassay by a double antibody method with a guinea pig antiserum (Bio-Makor, Jerusalem, Israel) and rat insulin as the standard. Corticosterone was assayed by a specific radioimmunoassay method [22]. Epinephrine and norepinephrine were measured by a high performance liquid chromatography method [23]. Aspartate aminotransferase (AST), alanine aminotransferase (ALT), total protein and albumin levels in plasma were determined with an autoanalyzer (Parallel™, American Monitor Corp., Indianapolis, U.S.A.). The increase in cAMP was represented as the area over the cAMP level in the effluent just before 10-min infusion of epinephrine.

The results are shown as the mean for 5 to 14 observations ± SEM. Wilcoxon's rank-sum test was used for analysis of differences between groups.

Results

Epinephrine-induced glucose output and cAMP release from BB/W rat liver

Basal glucose output from the perfused rat liver was 0.39 ± 0.04 µmol/g liver/min for normal Wistar rats and 0.29 ± 0.01 µmol/g liver/min for non-diabetic BB/W rats (Fig. 1A). When 1 µM epinephrine was infused for 10 min, it increased to a maximum of 2.24 ± 0.16 µmol/g liver/min for normal Wistar rats and 1.77 ± 0.19 µmol/g liver/min for non-diabetic BB/W rats at 3 min. In the adipose tissue-preserved diabetic BB/W rat liver, basal glucose output was greater than in the non-diabetic liver (0.48 ± 0.03 vs. 0.29 ± 0.01 µmol/g liver/min, P<0.01), but 1 µM epinephrine-induced glucose output at 3 min was similar in these two groups (1.63 ± 0.13 vs. 1.77 ± 0.19 µmol/g liver/min, NS). Basal glucose output from adipose tissue-absent diabetic liver was greater than that from non-diabetic liver (0.55 ± 0.06 vs. 0.29 ± 0.01 µmol/g liver/min, P<0.01), but not greater than that from adipose tissue-preserved diabetic liver (0.55 ± 0.06 vs. 0.48 ± 0.03 µmol/g liver/min, NS). Epinephrine (1 µM)-induced glucose output from adipose tissue-absent diabetic liver was less than those from both non-diabetic and adipose tissue-preserved diabetic livers (1.12 ± 0.12 vs. 1.77 ± 0.19 and 1.63 ± 0.13 µmol/g liver/min at 3 min, P<0.01, respectively).

Basal cAMP release from perfused rat liver was 1.33 ± 0.07 pmol/g liver/min for normal Wistar rats and 1.16 ± 0.11 pmol/g liver/min for non-
diabetic BB/W rats (Fig. 1B). When 1 μM epinephrine was infused for 10 min, it increased to a maximum of 4.03 ± 0.42 pmol/g liver/min for normal Wistar rats and 4.27 ± 0.54 pmol/g liver/min for non-diabetic BB/W rats at 2 min. Basal and 1 μM epinephrine-induced cAMP in the effluent did not differ from that in non-diabetic liver (1.38 ± 0.24 vs. 1.16 ± 0.11 pmol/g liver/min at 0 min, NS, and 2.96 ± 0.50 vs. 4.27 ± 0.54 pmol/g liver/min at 2 min, NS, respectively). Basal cAMP release in the effluent from adipose tissue-absent diabetic liver was greater than those from both non-diabetic and adipose tissue-preserved diabetic livers (2.78 ± 0.02 vs. 1.16 ± 0.11 and 1.38 ± 0.24 pmol/g liver/min, P<0.01, respectively). Epinephrine (1 μM)-induced cAMP release from adipose tissue-absent diabetic liver was much greater than those from both non-diabetic and adipose tissue-preserved diabetic livers, 141 ± 34 vs. 4.27 ± 0.54 and 2.96 ± 0.50 pmol/g liver/min at 2 min, P<0.01, respectively).

Profiles of BB/W and normal Wistar rats

There were no differences in age, body weight, ratio of liver weight to body weight (LW/BW), plasma glucose, insulin, aspartate aminotransferase (AST), alanine aminotransferase (ALT) and epinephrine-induced hepatic cAMP production (E-cAMP) between non-diabetic BB/W and normal Wistar rats (Table 1). Adipose tissue-preserved diabetic BB/W rats had higher plasma glucose and lower plasma insulin than non-diabetic BB/W rats. The age, body weight, ratio of liver weight to body weight (LW/BW), AST, ALT and E-cAMP of adipose tissue-preserved diabetic and non-diabetic BB/W rats did not differ significantly. The age of and AST in adipose tissue-absent diabetic BB/W rats were greater than those of non-diabetic BB/W rats but similar to those of adipose tissue-preserved diabetic BB/W rats. Body weight and plasma insulin concentration in adipose tissue-absent BB/W rats were lower than those in both adipose tissue-preserved diabetic and non-diabetic BB/W rats. Plasma glucose, ALT and E-cAMP in adipose tissue-absent diabetic rats were greater than those in both adipose tissue-preserved diabetic and non-diabetic BB/W rats (Table 1).

**Histological examination**

There was no or only minimal lymphocytic infiltration around a few arterioles or islets in the pancreas of non-diabetic BB/W rats. In the pancreas from adipose tissue-preserved diabetic BB/W rats, most islets were infiltrated and destroyed by lymphocytes, and periarteriolar lymphocytic accumulation was frequently observed. In pancreas from adipose tissue-absent diabetic BB/W rats, islets were destroyed and decreased in number and size, but no periarteriolar lymphocytic accumulation was observed.

Lymphocytic infiltration was also observed in the thyroid gland, but the frequency of infiltration was similar in all three groups of BB/W rats, being 54.5% (12/22) in non-diabetic, 50.0% (15/30) in the adipose tissue-present diabetic BB/W rats, 58.3% (15/26) in the adipose tissue-absent diabetic BB/W rats, and 54.5% (12/22) in the non-diabetic BB/W rats. The age, body weight, ratio of liver weight to body weight (LW/BW), plasma glucose (PG), insulin (IRI), aspartate aminotransferase (AST), alanine aminotransferase (ALT) and hepatic epinephrine-induced cAMP production (E-cAMP) in BB/W and normal Wistar rats (Table 1). Adipose tissue-preserved diabetic BB/W rats had higher plasma glucose and lower plasma insulin than non-diabetic BB/W rats.

Table 1. Age, body weight (BW), ratio of liver weight to body weight (LW/BW), plasma glucose (PG), insulin (IRI), aspartate aminotransferase (AST), alanine aminotransferase (ALT) and hepatic epinephrine-induced cAMP production (E-cAMP) in BB/W and normal Wistar rats

<table>
<thead>
<tr>
<th></th>
<th>Age (day)</th>
<th>BW (g)</th>
<th>LW/BW (%)</th>
<th>PG (mM)</th>
<th>IRI (pM)</th>
<th>AST (IU/L)</th>
<th>ALT (IU/L)</th>
<th>E-cAMP (pmol/g liver.20 min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal Wistar rats</td>
<td>75 ± 1 (11)</td>
<td>223 ± 4 (13)</td>
<td>3.5 ± 0.1 (13)</td>
<td>9.0 ± 0.4 (9)</td>
<td>352 ± 105 (8)</td>
<td>65 ± 4 (6)</td>
<td>34 ± 3 (6)</td>
<td>19.9 ± 4.2 (6)</td>
</tr>
<tr>
<td>Non-diabetic BB/W rats</td>
<td>87 ± 9 (11)</td>
<td>254 ± 17 (11)</td>
<td>3.7 ± 0.1 (11)</td>
<td>10.4 ± 0.4 (11)</td>
<td>433 ± 48 (5)</td>
<td>52 ± 5 (5)</td>
<td>20 ± 2 (5)</td>
<td>26.7 ± 3.8 (5)</td>
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<td>Diabetic BB/W rats</td>
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<tr>
<td>(adipose tissue-present)</td>
<td>112 ± 12 (14)</td>
<td>267 ± 7 (14)</td>
<td>3.6 ± 0.1 (14)</td>
<td>15.1 ± 1.8* (14)</td>
<td>201 ± 41* (14)</td>
<td>73 ± 12 (7)</td>
<td>35 ± 9 (7)</td>
<td>11.8 ± 3.9 (8)</td>
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<tr>
<td>(adipose tissue-absent)</td>
<td>126 ± 8** 183 ± 13*** 4.3 ± 0.3*</td>
<td>30.2 ± 2.1*** 39 ± 4*</td>
<td>350 ± 106 156 ± 44*</td>
<td>1127.7 ± 353.8***</td>
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E-cAMP is represented as the area over the cAMP level in the effluent just before 10-min infusion of 1 μM epinephrine. Number of observation is in parenthesis. * P<0.05; ** P<0.01; *** P<0.001; * vs. non-diabetic BB/W rats; ** vs. adipose tissue-present diabetic BB/W rats.
adipose tissue-preserved diabetic and 33.3% (9/27) in adipose tissue-absent diabetic BB/W rats, but no lymphocytic infiltration or destruction was observed on hematoxylin & eosin staining in the adrenal gland or the pituitary gland in the three groups of BB/W rats.

There was no lymphocytic infiltration in the liver of BB/W rats. The shape and size of hepatic lobules and hepatocytes were similar in the three groups on hematoxylin & eosin staining. The portal area was also intact, but the liver from adipose tissue-absent diabetic BB/W rats was only slightly PAS stained.

**Plasma hormone concentrations in BB/W rats**

Plasma concentrations of glucagon, epinephrine, norepinephrine, free thyroxine and corticosterone in BB/W and normal Wistar rats

<table>
<thead>
<tr>
<th></th>
<th>glucagon (ng/l)</th>
<th>epinephrine (nM)</th>
<th>norepinephrine (nM)</th>
<th>free thyroxine (pM)</th>
<th>corticosterone (nM)</th>
</tr>
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<tr>
<td>Normal Wistar rats</td>
<td>85 ± 12</td>
<td>0.98 ± 0.36</td>
<td>1.95 ± 0.70</td>
<td>27.4 ± 0.9</td>
<td>1125 ± 69</td>
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<td>(6)</td>
<td>(7)</td>
<td>(7)</td>
<td>(7)</td>
<td>(6)</td>
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<td>Non-diabetic BB/W rats</td>
<td>128 ± 60</td>
<td>0.66 ± 0.35</td>
<td>0.54 ± 0.23</td>
<td>24.5 ± 0.8*</td>
<td>833 ± 79*</td>
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<td>(8)</td>
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<tr>
<td>Diabetic BB/W rats</td>
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<tr>
<td>(adipose tissue-present)</td>
<td>143 ± 93</td>
<td>0.73 ± 0.29</td>
<td>1.17 ± 0.53</td>
<td>25.4 ± 6.5</td>
<td>524 ± 69*</td>
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<tr>
<td>(5)</td>
<td>(7)</td>
<td>(7)</td>
<td>(8)</td>
<td>(6)</td>
<td></td>
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<tr>
<td>(adipose tissue-absent)</td>
<td>123 ± 27</td>
<td>0.64 ± 0.31</td>
<td>2.24 ± 1.05</td>
<td>10.7 ± 1.4**</td>
<td>204 ± 68**</td>
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<td>(5)</td>
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<td>(8)</td>
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Table 2. Plasma concentrations of glucagon, epinephrine, norepinephrine, free thyroxine and corticosterone in BB/W and normal Wistar rats

Number of observation is in parenthesis. * P<0.05; ** P<0.01; * vs. non-diabetic BB/W rats; ** vs. adipose tissue-preserved diabetic BB/W rats; *** vs. normal Wistar rats.

**Plasma hormone concentrations in BB/W rats**

Plasma concentrations of glucagon, epinephrine, norepinephrine, free thyroxine and corticosterone in BB/W and normal Wistar rats

<table>
<thead>
<tr>
<th></th>
<th>free thyroxine (pM)</th>
<th>total protein (g/dl)</th>
<th>albumin (g/dl)</th>
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<tr>
<td></td>
<td>thyroiditis absent</td>
<td>thyroiditis present</td>
<td>thyroiditis absent</td>
</tr>
<tr>
<td>Normal Wistar rats</td>
<td>27.4 ± 0.9</td>
<td>5.5 ± 0.1</td>
<td>3.2 ± 0.1</td>
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<td>(7)</td>
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<tr>
<td>Non-diabetic BB/W rats</td>
<td>24.8 ± 1.6</td>
<td>4.9 ± 0.2*</td>
<td>2.7 ± 0.1**</td>
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<td>(7)</td>
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<tr>
<td>Diabetic BB/W rats</td>
<td>28.1 ± 7.7</td>
<td>4.5 ± 0.2</td>
<td>2.5 ± 0.1</td>
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<td>(adipose tissue-present)</td>
<td>21.5 ± 1.4</td>
<td>4.8 ± 0.3</td>
<td>2.6 ± 0.2</td>
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<td>(8)</td>
<td>(9)</td>
<td>(7)</td>
<td>(7)</td>
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<tr>
<td>(adipose tissue-absent)</td>
<td>9.1 ± 1.4*</td>
<td>3.6 ± 0.1**</td>
<td>2.0 ± 0.1**</td>
</tr>
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<td>(8)</td>
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Table 3. Comparison of plasma concentrations of free thyroxine, total protein and albumin in the presence and the absence of lymphocytic thyroiditis

Number of observation is in parenthesis. * P<0.05; ** P<0.01; * vs. lymphocytic thyroiditis-absent BB/W rats; ** vs. adipose tissue-present diabetic BB/W rats; *** vs. normal Wistar rats.

Plasma free thyroxine was slightly lower in non-diabetic BB/W rats than in normal Wistar rats, and was lowest in adipose tissue-absent diabetic BB/W rats (Table 2), but the thyroxine level did not differ significantly between BB/W rats with and without lymphocytic thyroiditis (Table 3). Plasma corticosterone was also lower in non-diabetic BB/W rats than in normal Wistar rats, and was lowest in diabetic BB/W rats (Table 2).

Plasma total protein and albumin levels were slightly lower in non-diabetic BB/W rats than in normal Wistar rats, and were lowest in adipose tissue-absent diabetic BB/W rats (Table 3).
Discussion

It has been confirmed that cAMP in the effluent reflects cAMP content in perfused liver [20, 21]. When epinephrine was infused, only a weak cAMP response was observed in the non-diabetic rat liver. These findings are consistent with the following reports. Catecholamines stimulate glucose output from male rat liver via α-adrenergic receptors [24]. Expression of the α-adrenergic receptor gene [25] but not of the β-adrenergic receptor gene [26] has been confirmed in the normal rat liver. In our previous study [9], cAMP response which was dose-dependently enhanced by catecholamines was observed only in the liver of adipose tissue-absent streptozotocin-induced diabetic rats. As expected, epinephrine-induced cAMP response was enhanced only in liver from adipose tissue-absent diabetic BB/W rats, so that the complete loss of intraperitoneal adipose tissue in addition to diabetes appeared to be required for enhancement of catecholamine-induced cAMP response in rat liver.

Basal cAMP release was increased only in the adipose tissue-absent diabetic BB/W rat livers. This might have been due to reduced insulin-mediated cAMP suppression [4], but it seems unlikely that lack of insulin is directly responsible for enhanced epinephrine-induced cAMP response, since glucagon-induced cAMP response was not enhanced in adipose tissue-absent diabetic BB/W rat livers (preliminary observation). On the other hand, basal glucose output from the liver was greater in both adipose tissue-preserved and -absent diabetic BB/W rats than in non-diabetic BB/W rats. This is consistent with human diabetes [1, 2], but epinephrine-induced glucose output was low in adipose tissue-absent diabetic rat liver. This may have been due to depletion of glycogen, since the adipose tissue-absent diabetic rat liver was only slightly stained on PAS staining. It has been established that epinephrine-induced glucose output is derived mainly from glycogenolysis when the liver is perfused without gluconeogenic substrates [18].

The reduction in plasma epinephrine has been regarded as causing increased β-adrenergic response in the hypothalamic-lesioned rat liver [18]. In severe diabetes with neuropathy, enhanced response to catecholamine has been known as denervation supersensitivity [5, 27], but denervation supersensitivity is not likely to be the reason for the enhanced epinephrine-induced cAMP response in the adipose tissue-absent diabetic BB/W liver, since plasma epinephrine and norepinephrine levels in the three groups of BB/W rats did not differ significantly.

The plasma free thyroxine concentration was low in the adipose tissue-absent diabetic BB/W rats. In hypothyroid rat livers, enhanced β-adrenergic activation of glycogen phosphorylase has been reported [14, 15], so that the enhanced epinephrine-induced cAMP response may be due to hypothyroidism caused by lymphocytic thyroiditis. Nevertheless, the prevalence of thyroiditis was similar in all three groups of BB/W rats, and the plasma free thyroxine concentration was similar in BB/W rats with and without lymphocytic thyroiditis as previously reported [19, 28], so that lymphocytic thyroiditis cannot account for the low plasma free thyroxine concentration observed in adipose tissue-absent diabetic BB/W rats. On the other hand, plasma total protein and albumin concentrations were low in adipose tissue-absent diabetic BB/W rats. This suggests that thyroxine-binding proteins are decreased in the plasma of adipose tissue-absent diabetic BB/W rats. Although the plasma-free thyroxine level is less affected by thyroxine-binding proteins, it is known that the plasma-free thyroxine concentration obtained by a direct radioimmunoassay is frequently low in severe non-thyroidal illness [29]. A low plasma concentration of thyroxine-binding globulin was reported in untreated human diabetes [30]. It is therefore likely that the low plasma free thyroxine concentration observed in adipose tissue-absent diabetic BB/W rats resulted from severe diabetes.

The plasma corticosterone concentration was low in BB/W rats. Since BB/W rats have an autoimmune diathesis in addition to insulitis and thyroiditis [31], the pituitary and adrenal glands were examined histologically, but no lymphocytic infiltration was found in either gland. This is consistent with a report stating that the adrenal gland was unaffected in BB/W rats [32]. Most corticosterone in the plasma is bound to corticoid-binding globulin and albumin [33]. Since the low plasma total protein and albumin levels were
observed in BB/W rats, the low plasma corticosterone concentration seemed to reflect reduced plasma levels of corticoid-binding proteins, and the low plasma corticosterone concentration was therefore not likely to be responsible for the enhanced $\beta$-adrenergic response in the adipose tissue-absent diabetic BB/W rat liver, although enhanced $\beta$-adrenergic response has also been reported in adrenalectomized rat livers [16, 17]. 

When streptozotocin-induced diabetic rats were kept without insulin, liver dysfunction was observed [9]. Streptozotocin is known to be hepatotoxic [10]. Surprisingly, liver dysfunction was observed on blood chemistry testing in adipose tissue-absent diabetic BB/W rats, but not when adipose tissue was preserved. In adipose tissue-absent diabetic BB/W rats, LW/BW was high, but no remarkable histological change was observed, so that the liver dysfunction observed in adipose tissue-absent diabetic BB/W rats appeared to differ from that in streptozotocin-induced diabetic [9, 10], partially hepatectomized [11] and cholestatic [12] rats. In adipose tissue-absent diabetic BB/W rats, plasma glucose was higher, plasma insulin was lower, and islet destruction was greater than in adipose tissue-preserved diabetic BB/W rats. These findings suggested that loss of adipose tissue resulted from severe diabetes. On the other hand, the severity of diabetes and the amount of adipose tissue can vary continuously, but epinephrine-induced cAMP response and liver dysfunction were not a continuous phenomenon in diabetic BB/W rats. When adipose tissue was lost completely, ketogenesis was abruptly reduced. Severe diabetes with a loss of adipose tissue appeared to cause significant changes in the metabolism and enhanced $\beta$-adrenergic response in the liver.

References


