Impaired stimulation of intestinal glucose absorption via hepatoenteral nerves in streptozotocin-diabetic rats

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Impaired stimulation of intestinal glucose absorption via hepatoenteral nerves in streptozotocin-diabetic rats. Am. J. Physiol. 277 (Gastrointest. Liver Physiol. 40): G285–G291, 1999.—In an ex situ organ perfusion system, that of the isolated nonrecirculating joint perfusion of rat small intestine and liver, insulin infused into the portal vein increased intestinal glucose absorption. This insulin action against the bloodstream can be blocked by TTX, indicating a propagation of the insulin signal via hepatoenteral nerves, which conforms with previous studies with atropine and carbachol. Insulin action could also be mimicked by dibutyryl cAMP (DBcAMP) acting directly on the absorptive enterocytes. Because autonomic neuropathy is a common late complication of diabetes mellitus, the possible impairment of these nerves in the diabetic state was studied in streptozotocin-diabetic rats. In the isolated joint intestine-liver perfusion, glucose was applied as a bolus into the lumen; its absorption was measured in the portal vein. In 5-day diabetic as well as in control rats, portal insulin, arterial carbachol, and arterial DBcAMP increased intestinal glucose absorption. In 3-mo diabetic rats portal insulin and arterial carbachol failed to stimulate glucose absorption, whereas arterial DBcAMP still did so, indicating an undisturbed function of the absorptive enterocytes. The lack of an effect of portal insulin and arterial carbachol and the unchanged action of DBcAMP in the chronically diabetic rats indicated that the signaling chain via the hepatoenteral nerves was impaired, which is in line with a diabetic neuropathy.

diabetic neuropathy; autonomic nervous system; cholinergic nerves

In the developed world carbohydrates contribute 50% of the daily intake of calories (4). After digestion of the dietary poly- and oligosaccharides, monosaccharides are absorbed via different transport systems: glucose is taken up into the enterocyte from the intestinal lumen via the sodium-dependent glucose transporter 1 (SGLT1) located in the apical membrane and released from the enterocyte to the circulation via the sodium-independent glucose transporter 2 (GLUT2) of the basolateral membrane (7). These transport steps are widely believed not to be acutely regulated. However, there is growing evidence now for a short-term regulation of intestinal glucose absorption in several different experimental systems (5, 6, 16, 18, 19). Recently, an acute stimulation of intestinal glucose absorption was demonstrated in an ex situ organ perfusion system, the isolated nonrecirculating joint perfusion of small intestine and liver of the rat. In this experimental system, insulin, infused into the portal vein (PV), increased intestinal glucose absorption to 250% within 3 min (18). This stimulatory effect of portal insulin on the intestine was inhibited by atropine and mimicked by carbachol injected into the superior mesenteric artery (SMA; Ref. 18). These findings showed that insulin was sensed in the hepatoportal area and that a signal was transmitted against the bloodstream to the enterocytes via hepatoenteral (from liver to intestine) cholinergic nerves.

Neuropathy, along with microangiopathy and retinopathy, represents one of the most common late complications of diabetes mellitus (8, 21). Distal sensory neuropathy is the predominant symptom (15), found in 34% of insulin-dependent diabetic patients (IDDM) and in 26% of non-insulin-dependent diabetic patients (NIDDM) (10, 22). In addition, diabetes mellitus also affects the autonomic nervous system. An autonomic neuropathy was found in 17–22% of patients with IDDM or NIDDM (23). In functional studies with streptozotocin-diabetic rats, a loss of Na1-K1-ATPase activity in the vagus nerve (12) and an impairment of the stimulation of hepatic glucose output by sympathetic hepatic nerves (17) were observed, indicating diabetic neuropathy.

Thus it was the aim of the present investigation to confirm that the insulin-signaling chain from the liver to the intestine involved hepatoenteral nerves and to examine a possible functional impairment of the signaling chain in chronically streptozotocin-diabetic rats in line with a diabetic neuropathy.

MATERIALS AND METHODS

Materials. All chemicals were of reagent grade and from commercial sources. Enzymes were purchased from Boehringer (Mannheim, Germany); insulin, carbachol, and streptozotocin were from Sigma (Munich, Germany); and TTX was from Roth (Karlsruhe, Germany). BSA, dextran, and DBcAMP were delivered by AppliChem (Darmstadt, Germany).

Animals. Male Wistar rats were obtained from Harlan-Winkelmann (Borchen, Germany). They were kept on a 12-h day-night rhythm with free access to food (standard diet; Ssniff, Soest, Germany) and water. For the induction of diabetes mellitus, rats (100–120 g body wt) were starved for 24 h, followed by an intraperitoneal injection of streptozotocin (50 mg/kg body wt, 33 g/l dissolved in 50 mmol/L sodium citrate at pH 4.5). Animals were then fed the standard diet (Ssniff) ad libitum. Control rats were weight matched to the body weight of the chronically diabetic animals following the 3-mo period of diabetes. In addition, to exclude a possible neurotoxicity of streptozotocin, 5-day diabetic animals were examined. During the preparation of the joint perfusion of

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small intestine and liver, blood and urine samples were obtained for subsequent determination of the glucose concentration. Treatment of animals followed the German Law on the Protection of Animals and was performed with permission from the state animal welfare committee.

Preparation of the isolated joint perfusion of small intestine and liver. The joint perfusion of small intestine and liver was performed as previously described (5, 18). Rats were anesthetized by intraperitoneal injection of pentobarbital sodium (40 g/l in 0.9% NaCl; 60 mg/kg body wt). A midline laparotomy was performed, and the SMA and the celiac trunk (CT) were cannulated. After the immediate incision of the inferior vena cava (IVC), a nonrecirculating perfusion of intestine and liver was started at a hydrostatic pressure of 120 cmH2O (i.e., 88 mmHg \( \approx 11.77 \) kPa). Then, spleen and the proximal half of the stomach were removed, and, for the luminal glucose application, a plastic catheter was introduced through the pyloric sphincter into the proximal duodenum. The cecum was incised, and the content of the small intestine was gently washed out with a warmed saline solution. Afterward, a cannula for the vascular outflow was introduced into the right atrium, and the tip was positioned at the inflow of the hepatic vein into the IVC and fixed. Then, intestine and liver were transferred into an organ bath filled with a warmed saline solution, and two flexible catheters were introduced into the PV, one for obtaining medium samples and the other one for infusion of insulin.

Determination of vascular flow. The flow rate in the SMA was measured with an ultrasound flowmeter T106 (Transonic Systems, Ithaca, NY). Total flow in the IVC was quantified by fractionated sampling of the effluent into calibrated tubes. The flow rate in the CT was calculated as the difference between the flow into the IVC and the SMA.

Perfusion medium, vascular application of effectors, and intestinal glucose bolus. The perfusion medium consisted of a Krebs-Henseleit buffer containing (in mmol/l) 5.0 glucose, 2.0 lactate, 0.2 pyruvate, and 1.0 glutamine, with 1% wt/vol BSA and 3% wt/vol dextran. The perfusion medium was equilibrated with a gas mixture of 19 O2:1 CO2. Insulin (final concentration 100 nmol/l), carbachol (final concentration 10 µmol/l), dibutyryl cAMP (DBcAMP; final concentration 1 µmol/l), or TTX (final concentration 1 µmol/l) were infused as solutions in perfusion medium into the vessels as described in the legends of Figs. 1–4. The luminal glucose bolus (1 g diluted in 1.5 ml 0.9% NaCl) was applied within 1 min via the catheter placed in the duodenum.

Determination of glucose concentration. Perfusion samples were taken every 1 min and immediately chilled on ice. Glucose concentration was measured with the use of a standard enzymatic technique with glucose dehydrogenase (Merck system; Ref. 1). Blood and urine concentrations were determined with a glucose analyzer (model 2; Beckman, Munich, Germany) by the glucose oxidase method.

Statistical analysis. All results are represented as means \( \pm \) SE for the indicated number of experiments. Data were analyzed by Student’s t-test for unpaired data. P < 0.05 was considered significant.

### RESULTS

Characterization of acutely and chronically diabetic rats. Rats were injected with streptozotocin after 24-h starvation to induce a diabetic state. All treated rats developed clinical signs of hyperglycemia, e.g., polydipsia or polyuria within 2–3 days. They were kept for 5 days or 3 mo before they were used for the preparation of the jointly perfused small intestine and liver. As a simple measure of the diabetic state, glucosuria was examined from day 3 onward. At day 5, all streptozotocin-treated rats had developed severe glucosuria (Table 1). In addition, during the operative procedure, blood samples were obtained to confirm the diabetic state. A profound rise in the blood glucose concentration was observed at 5 days as well as 3 mo after streptozotocin treatment (Table 1). During the preparation it became obvious that in the chronically diabetic animals, the weight of the small intestine was enhanced by 72%, in line with a diabetic enteropathy (Table 1). Most of the chronically diabetic animals at the end of the 3-mo period showed another late complication of diabetes, i.e., visual impairment (detected by inspection of dim lenses).

Inhibition by TTX of the portal insulin-induced but not the cAMP-induced increase in intestinal glucose absorption. In all experiments, the first luminal glucose bolus (1 g) was applied without infusion of any effectors. Under this condition, the basal rate of glucose absorption reached a maximum of 3.6 \( \pm \) 0.7 µmol·min\(^{-1}\)·g organ wt\(^{-1}\) (Fig. 1). With an infusion of insulin (100 nmol/l) into the PV, intestinal glucose absorption following the second glucose bolus after a 25-min interval was increased to a maximal rate of 14.4 \( \pm \) 1.7 µmol·min\(^{-1}\)·g organ wt\(^{-1}\) (Fig. 1). In the presence of insulin, glucose absorption following the third glucose bolus after a 20-min interval (1 g) was elevated again to 13.8 \( \pm \) 2.1 µmol·min\(^{-1}\)·g organ wt\(^{-1}\) (not shown). If the third glucose bolus (1 g) was applied in the presence of portal insulin and with an additional infusion of the sodium channel blocker TTX (1 µmol/l; Ref. 14) into the SMA, peak glucose absorption amounted to a maximum of 3.7 \( \pm \) 0.5 µmol·min\(^{-1}\)·g organ wt\(^{-1}\) as in the controls (Fig. 1). In another series of experiments, basal glucose absorption after the first glucose bolus equaled that of the first series of experiments, and glucose absorption following the second glucose bolus was increased by arterial infusion of DBcAMP (1 µmol/l) to 15.3 \( \pm \) 4.8 µmol·min\(^{-1}\)·g organ wt\(^{-1}\) (data not shown). If the second glucose bolus was applied in the presence of DBcAMP (1 µmol/l) along with arterial infusion of TTX (1 µmol/l), glucose absorption after the second glucose bolus was not impaired and reached a maximal rate of 16.2 \( \pm \) 5.7 µmol·min\(^{-1}\)·g organ wt\(^{-1}\) (Fig. 1). The inhibition of the action of portal insulin but not of arterial DBcAMP by TTX confirms the conclusion from

### Table 1. Characterization of control and streptozotocin-diabetic rats

<table>
<thead>
<tr>
<th></th>
<th>Control (n = 4)</th>
<th>Diabetes Mellitus, 5 days (n = 4)</th>
<th>Diabetes Mellitus, 3 mo (n = 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body wt, g</td>
<td>337.2 ( \pm ) 18.6</td>
<td>327.5 ( \pm ) 22.5</td>
<td>348.8 ( \pm ) 37.5</td>
</tr>
<tr>
<td>Blood glucose, mmol/l</td>
<td>8.5 ( \pm ) 2.3</td>
<td>23.8 ( \pm ) 1.8*</td>
<td>26.3 ( \pm ) 1.1*</td>
</tr>
<tr>
<td>Urine glucose, mmol/l</td>
<td>ND</td>
<td>54.3 ( \pm ) 16.3*</td>
<td>71.1 ( \pm ) 19.3*</td>
</tr>
<tr>
<td>Intestinal wt, g</td>
<td>7.2 ( \pm ) 0.9</td>
<td>7.1 ( \pm ) 0.8*</td>
<td>12.4 ( \pm ) 1.1*</td>
</tr>
</tbody>
</table>

Values are means \( \pm \) SE; n = no. of animals. *P < 0.05. ND, not detectable.
experiments with atropine and carbachol (Ref. 18; cf. the introduction) that the signal elicited by portal insulin in the hepatoporal area was transmitted to the intestine against the bloodstream via hepatointestinal nerves.

Loss of portal insulin-induced increase in intestinal glucose absorption in chronically diabetic rats. After the first glucose bolus without infusion of effectors, the ensuing basal rate of glucose absorption reached a maximum of 2.6 ± 1.1 µmol·min⁻¹·g organ wt⁻¹ in the control group (Fig. 2). The total absorption of glucose (in µmol) during the first 10 min after the glucose bolus was determined as the area under the absorption vs. time curve (µmol·min⁻¹·g⁻¹ × min) multiplied by the organ weight (g). In control animals, total basal glucose absorption amounted to 281 ± 31 µmol. In chronically diabetic animals, the basal rate of glucose absorption reached a maximum of 1.7 ± 0.5 µmol·min⁻¹·g organ wt⁻¹ (Fig. 2), corresponding to a total basal glucose absorption of 228 ± 30 µmol. Total basal glucose absorption was similar in the two groups of animals because the small intestine weight of the diabetic animals was 23% larger than that of the controls (Table 1). Total basal glucose absorption in the acutely diabetic animals was not different from that of control rats (276 ± 22 µmol). For a better comparison, total basal glucose absorption was taken as 100% in each of the three experimental groups (Fig. 3).

In the control group, insulin (100 nmol/l) infused into the PV increased the rate of glucose absorption from a maximum of 2.6 ± 1.1 to a maximum of 12.6 ± 4.6 µmol·min⁻¹·g organ wt⁻¹ (Fig. 2); total insulin-stimulated glucose absorption was raised from basal 281 ± 31 to 737 ± 66 µmol, representing an increase to 262% (Fig. 3). In chronically diabetic rats, portal insulin did not significantly raise the rate of intestinal glucose absorption (Fig. 2); the calculated total glucose absorption was 254 ± 41 µmol with insulin, compared with 228 ± 30 µmol without insulin (Fig. 3). Thus the stimulatory effect of portal insulin, which is mediated via hepatointestinal cholinergic nerves (18), was abrogated in chronically diabetic rats (Fig. 2). In acutely diabetic rats, the stimulatory effect of portal insulin on intestinal glucose absorption was unimpaired (Fig. 3).

The flow rates in the SMA and CT remained essentially constant during the entire experiments in the three groups of animals, although the total flow was 31 to 737 µmol during the first 10 min after the glucose bolus was determined as the area under the absorption vs. time curve (µmol·min⁻¹·g⁻¹ × min) multiplied by the organ weight (g). In control animals, total basal glucose absorption amounted to 281 ± 31 µmol. In chronically diabetic animals, the basal rate of glucose absorption reached a maximum of 1.7 ± 0.5 µmol·min⁻¹·g organ wt⁻¹ (Fig. 2), corresponding to a total basal glucose absorption of 228 ± 30 µmol. Total basal glucose absorption was similar in the two groups of animals because the small intestine weight of the diabetic animals was 23% larger than that of the controls (Table 1). Total basal glucose absorption in the acutely diabetic animals was not different from that of control rats (276 ± 22 µmol). For a better comparison, total basal glucose absorption was taken as 100% in each of the three experimental groups (Fig. 3).

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The flow rates in the SMA and CT remained essentially constant during the entire experiments in the three groups of animals, although the total flow was ~1 ml·min⁻¹·g organ wt⁻¹ lower in the chronically diabetic rats than in the control rats (Fig. 2, bottom) and acutely diabetic animals (not shown). However, because of the higher organ weight (Table 1), the absolute flow rates were even a little higher in the chronically diabetic animals, i.e., 29.8 vs. 24.5 ml/min.

Loss of carbachol-induced but not of DBcAMP-induced increase in intestinal glucose absorption in chronically diabetic rats. The loss of the portal insulin-induced increase in intestinal glucose absorption in the 3-mo diabetic animals could be due to an impairment of the hepatointestinal cholinergic nerves and/or of the absorptive capacity of the enterocytes. When applied via the SMA, carbachol, a muscarinic receptor agonist (18), and DBcAMP (6, 16, 19), a membrane-permeable cAMP analog, have been shown to mimic the stimulatory effect of portal insulin on glucose absorption in the small intestine. Therefore, in another series of experiments, the stimulatory effects of arterial carbachol and DBcAMP were examined to distinguish between a functional impairment of the hepatointestinal nerves or a deterioration of the absorptive capacity of the enterocytes.

DBcAMP (10 µmol/l) infused into the SMA caused an increase in total glucose absorption to 828 ± 48 µmol in
control animals. Compared with the basal glucose absorption of 281 ± 31 µmol, this DBcAMP-elicited elevation amounted to 295% (Fig. 4). In 3-mo diabetic rats, total glucose absorption was raised by DBcAMP to 547 ± 697 µmol, which represented a significant increase to 240% compared with the unstimulated glucose absorption of 228 ± 30 µmol (Fig. 4). In acutely diabetic rats, DBcAMP stimulated glucose absorption to 262% (Fig. 4).

Carbachol (10 µmol/l) infused into the SMA induced a rise in total glucose absorption to 624 ± 51 µmol in the control group. Compared with the basal glucose absorption of 281 ± 31 µmol, this was an increase to 222% (Figs. 2 and 4). However, in 3-mo diabetic rats the stimulatory effect of carbachol was nearly completely abolished; glucose absorption was increased only insignificantly from 228 ± 30 to 294 ± 64 µmol or 128% (Figs. 2 and 4). In the acutely diabetic rats, carbachol significantly increased glucose absorption from 276 ± 22 to 554 ± 63 µmol, equaling 201% (Fig. 4). These results allow the conclusion that, in the chronically diabetic rats, the absorptive capacity of the enterocytes...
was essentially intact, whereas the signaling chain "portal insulin-hepatoenteral nerves-enterocytes-glucose absorption" was impaired.

DISCUSSION

Unaltered capacity for intestinal glucose absorption in chronically streptozotocin-diabetic rats. Glucose absorption in the small intestine occurs via two transporters: the sodium-dependent glucose transporter SGLT1 in the apical membrane and the sodium-independent glucose transporter GLUT2 in the basolateral membrane (4). In the present investigation, the increase in total glucose absorption after application of a bolus of 1 g into the lumen of the jointly perfused small intestine and liver of the rat was in the same range in control, 5-day acutely diabetic, and 3-mo chronically diabetic animals, both under basal unstimulated conditions and after stimulation by DBcAMP. With the experimental system used here, the isolated jointly perfused small intestine and liver of the rat, the capacity of the small intestine for glucose absorption was not altered in the diabetic state under basal and stimulated conditions. The unchanged basal absorption may be in contrast to data obtained in isolated segments of the small intestine of streptozotocin-diabetic rats (3); here the rate of glucose but not of galactose absorption was slightly increased. However, this isolated increase in glucose absorption is not easy to understand, because glucose and galactose are both absorbed via the same transporters, SGLT1 and GLUT2 (4). In autoradiographic examinations, this enhancement was found to be due to an increase in the number of transporters (3), which was confirmed in brush-border membrane vesicles of enterocytes (13). In conclusion, the present and the previous study (3) have shown that the glucose-absorptive capacity of the small intestine is unaltered or slightly increased but not impaired in the diabetic state.

Involvement of hepatoenteral nerves in the signaling chain for the stimulation by portal insulin of intestinal glucose absorption. In previous examinations with the isolated jointly perfused small intestine and liver of the rat, the stimulation by portal insulin of intestinal glucose absorption could be completely blocked by an infusion of atropine into the SMA and mimicked by arterial carbachol (18). Therefore, it was concluded that the signal pathway from the PV to the small intestine involved hepatoenteral cholinergic nerves. To confirm this conclusion, an additional series of experiments was performed using the neurotoxin TTX, which blocks sodium channels of axons and other excitable membranes (14). In the isolated jointly perfused small intestine and liver of the rat, TTX, infused into the SMA, entirely prevented the portal insulin-stimulated increase in intestinal glucose absorption (Fig. 1). Because TTX did not alter the increased glucose absorption after arterial infusion of DBcAMP, a direct effect of TTX on the absorptive process can be excluded (Fig. 1). These data support the previous results, which indicated the involvement of hepatoenteral nerves.

Impaired function of the signaling chain involving hepatoenteral nerves in chronically streptozotocin-diabetic rats. The stimulatory effect of portal insulin and arterial carbachol on glucose absorption was com-
completely abolished in 3-mo chronically diabetic but not in 5-day acutely diabetic rats (Figs. 2–4). Apparently, the signaling chain from the liver to the intestine involving hepatointestinal nerves was impaired. The anatomic basis of the hepatointestinal nerves mediating the enhancement of intestinal glucose absorption by portal insulin is unknown so far. The signaling chain must start with the sensing of insulin in the portal vein or liver tissue. Such a sensing of insulin has been described before using electrophysiological methods; in the superfused isolated portal vein of the rat, the addition of insulin to the superfusate caused an increase in the discharge rate of the afferent vagus nerve to the central nervous system (11). Therefore, it is very possible that the hepatointestinal nerves between liver and small intestine originate in the hepatopancreatic area and end in the small intestine, where they would release ACh to a cell carrying muscarinic receptors. Because cAMP is the intracellular messenger in the enterocytes stimulating glucose absorption (6, 16, 19), and because muscarinic receptors are known to increase inositol 1,4,5-trisphosphate or to decrease cAMP but not to elevate cAMP (2), ACh cannot act directly on the enterocytes. The intermediate cells between the hepatointestinal nerve cells and the enterocytes are not yet known. Because DBCAMP still increased glucose absorption in the isolated perfused small intestine and liver of chronically diabetic rats, the absorptive function of the enterocytes was not impaired. Thus the loss of the stimulatory effect of portal insulin and arterial carbachol was due to a defect of the intermediate cells and/or of the hepatointestinal nerve cells.

The hepatointestinal nerves must comprise an insulin sensory function, which could be a defect due to an insulin resistance. Because an insulin resistance can be detected very early in the diabetic state, e.g., within 6–8 h in 3T3-L1 adipocytes (20), the preserved action of portal insulin in 5-day acutely diabetic rats makes this mechanism rather unlikely. Thus the signaling chain involving hepatointestinal nerves and intermediate cells was impaired mainly in its ACh-dependent effector branch. This impairment corresponds to a neuropathy. A diabetic neuropathy is a well-known late complication of diabetes mellitus in diabetic patients (8, 10, 15, 21, 22, 23). In addition, a loss of function of autonomic nerves and impairment of Na\(^+\)-K\(^-\) ATPase in the vagus (12) and of glucose output from the liver after sympathetic nerve stimulation (17) have been shown before in 3-mo streptozotocin diabetic rats.

Possible pathophysiological role of the impairment of the signaling chain via hepatointestinal nerves in diabetes mellitus. In diabetes mellitus, postprandial glucose cannot be handled adequately by the organism, resulting in severe hyperglycemia. This is mainly because of a decrease in the rate of the insulin-stimulated glucose disappearance via utilization in skeletal muscle, adipose tissue, and liver. The loss of function of the hepatointestinal nerves, and thus of the portal insulin-stimulated glucose absorption, would lower the rate of glucose appearance and therefore smooth the postprandial increase in blood glucose concentration. Thus, in the diabetic state, the impaired signaling via the hepatointestinal nerves mediating the increase in glucose absorption by portal insulin could constitute an advantage of diabetic patients: the adjustment of the rate of glucose appearance and disappearance on a lower level should contribute to reduce postprandial hyperglycemia.

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REFERENCES


