Diarrhea in Streptozocin-treated Rats

Loss of Adrenergic Regulation of Intestinal Fluid and Electrolyte Transport

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Abstract

Diarrhea was noted in rats with streptozocin-induced chronic diabetes. We have investigated the possibility that this diarrhea is a consequence of altered neuronal control of water and electrolyte absorption in the intestinal epithelium. In particular, we examined noradrenergic control because alpha-2-adrenergic agonists are known to stimulate intestinal fluid absorption. When compared with nondiabetic littermates, chronically diabetic rats exhibited significant impairment of fluid absorption by the ileum and colon, but not the jejunum. This impairment of intestinal fluid absorption was not found in either insulin-treated or untreated acutely diabetic (7 d) animals. Mucosal histology appeared normal in all of the above groups.

Mucosal norepinephrine stores in the jejunum and ileum of chronically diabetic rats were estimated in vitro by the short-circuit current (Isc) response to tyramine, an agent that effectively releases stored norepinephrine. Pargyline was added to inhibit enzymatic destruction of the added tyramine. In chronically diabetic rats, the Isc response to tyramine was significantly decreased in ileum, but not in jejunum. However, when these responses were expressed as a fraction of the maximal Isc tissue response to exogenously added epinephrine, significant decreases were noted in both ileum and jejunum. In tissues from acutely diabetic rats, Isc responses to tyramine and epinephrine were no different from controls.

When sympathetic denervation was produced in nondiabetic rats by treatment with 6-OH-dopamine, the pattern of impaired fluid absorption that developed was the same as that observed in chronically diabetic rats. We conclude that impaired intestinal mucosal absorption of fluid and electrolytes slowly develops in rats made diabetic with streptozocin and that this absorptive impairment is due to a loss of normally present noradrenergic innervation of enterocytes.

Introduction

Diarrhea is one of several intestinal disorders reported to occur in diabetic patients. It has proved to be especially problematic because of its incapacitating nature and refractoriness to therapy with conventional antidiarrheal modalities. Characteristically, diabetics with this diarrhea are young to middle-aged, poorly controlled, insulin requiring, and have peripheral or autonomic neuropathy (1). They have minimal or no fat malabsorption (2) and normal mucosal histology (3, 4). The diarrhea has been attributed to disturbed gastrointestinal motility, but convincing evidence for this has been lacking (5, 6). In this study of streptozocin-treated rats, we explored the possibility that diarrhea can occur in diabetics as a consequence of altered neuronal control of water and electrolyte transport by the intestinal epithelium. A loss of adrenergic "tone" could result in diarrhea since stimulation of alpha-2 receptors on enterocytes promotes Na and Cl absorption and inhibits Cl and HCO_3 secretion (7, 8).

Methods

Induction of diabetes. Male Lewis rats (250–350 g; Harlan Sprague Dawley, Inc., M. A. Laboratory Animals & Teklad Diets, Indianapolis, IN) were made diabetic with streptozocin (60 mg/kg; The Upjohn Co., Kalamazoo, MI) administered via a dorsal tail vein. Diabetic and age-matched control animals were maintained on standard rat chow ad lib. A drop of blood was taken periodically from the dorsal tail vein for glucose determinations. A reflectance photometer and glucose reagent strips (Miles Ames Div., Miles Laboratories, Inc., Elkhart, IN) were used to make these determinations. Total glycosylated hemoglobins were measured by the thiobarbituric acid method (9) on blood obtained by cardiac puncture immediately after animals were killed. These determinations for our acutely diabetic (AD)[1] and chronically diabetic (CD) rats were similar to results obtained by Blanc et al. (10) in diabetic rats using high pressure liquid chromatography. AD and CD rats were defined as animals with persistent hyperglycemia (>400 mg/d) for 1 wk and 4–6 mo, respectively. The AD group treated with porcine lente insulin (Eli Lilly Co., Indianapolis, IN) received daily subcutaneous injections to maintain normoglycemia and normal levels of glycosylated hemoglobin.

In vivo studies

Measurements of intestinal fluid absorption. Rats were anesthetized with ether and maintained at 37°C. A midline abdominal incision was made, and the intestinal tract was ligated at three points: the ligament of Treitz, the ileo-cecal junction, and the colono-cecal junction. Incisions through the gut wall were made just distal to the highest and lowest ligatures and just proximal to the middle ligature. Cannulae were inserted through the most proximal and distal incisions, and the luminal contents were flushed out with warm 0.9% NaCl. The residual saline was emptied by gentle manual expression. Three intestinal loops of ~15 cm were created with ligatures in the jejunum beginning 2 cm distal to the ligament of Treitz, in the distal ileum beginning 4 cm proximal to the ileo-cecal valve and extending abroad, and in the

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1. *Abbreviations used in this paper:* AD, acutely diabetic; CD, chronically diabetic; Isc, short-circuit current; ΔIsc-max, Isc response to exogenously added epinephrine; ΔIsc-tyr, Isc response to tyramine; 6-OHDA, 6-hydroxydopamine.

colon beginning at the peritoneal reflection and extending proximally to 2 cm below the cecal-colonic junction. Loops were ligated without compromising mesenteric integrity or vascular and neuronal continuity. 2 ml of 0.9% saline prewarmed to 37°C was instilled into each empty loop through a 27-gauge needle inserted obliquely through the outer muscle layer. No fluid leakage was detected, and loops were only mildly distended. Viscera were returned to the abdominal cavity, the incision closed, and animals were allowed to recover from anesthesia. Less than 5 min transpired between instillation of fluid and abdominal closure. 60 min after closure, animals were killed with an overdose of ether and their gut loops removed. After their lengths were measured, loops were weighed, emptied, and reweighed to determine their residual intraluminal volumes (assuming 1 ml = 1 g). They were then dried to constant weight in a 50°C oven (~12 h). Results were expressed as the differences between initial and residual luminal loop volumes per centimeter or per gram.

Sympathectomy using 6-hydroxydopamine (6-OHDA). Using a modification of the method of Tapper et al. (11), normal littermates of the CD group were given a single dose of 6-OHDA (10 mg/kg dissolved in 0.9% saline and 1% ascorbic acid) through the dorsal tail vein. 3 d later fluid movement was measured as described above.

In vitro studies

Solution employed. In all in vitro experiments the solution used for bathing tissues contained the following in millimoles per liter: Na, 144; K, 5; Ca, 1.25; Mg, 1.1; Cl, 125; HCO_3, 25; H_2PO_4, 0.3; HPO_4, 1.65 (HCO_3-Ringer). This solution was gassed with 5% CO_2 in O_2. At 37°C it had a pH of 7.4. Intestinal segments of 2–3 cm were stripped of their serosa and underlying longitudinal muscle layer and mounted in Ussing chambers as previously described (12). Tissues were bathed on both sides with HCO_3-Ringer which was maintained at 37°C and circulated by gas lift. D-glucose (40 mmol/liter) was added to the serosal side, and an equimolar amount of mannitol was added to the mucosal side. Transmural potential difference, resistance, and short-circuit current (Isc) were determined as previously described (12).

Response to tyramine. Norepinephrine stores in jejunal and ileal mucosa were estimated by the Isc response to the serosal addition of 10 μmol/liter tyramine which, at that concentration, effectively releases ~80% of all stored norepinephrine (11). The monoamine oxidase inhibitor pargyline (50 μmol/liter) was added to the serosal side 10 min before tyramine to prevent metabolism of tyramine (11). 1.0 mmol/liter theophylline was added to the serosal reservoir 15 min before tyramine to stimulate tissues to secrete, thus maximizing the Isc responses to tyramine and epinephrine (see below). Immediately after Isc response to tyramine (ΔIsc-tyr) was recorded, the additional decrease in Isc produced by serosal addition of *l*-epinephrine (5.5 μmol/liter; Parke, Davis & Co., Detroit, MI) was recorded to determine the full capacity of the tissue to respond to catecholamines. Both responses to tyramine and to epinephrine could be completely reversed by the serosal addition of yohimbine (10 μmol/liter), indicating that alpha-2-adrenergic receptors were responsible for the observed decreases in Isc (7). A representative experiment is shown in Fig. 1. After reaching the response to epinephrine, 20 mmol/liter D-glucose was added to both reservoirs and the resulting increase in Isc determined as a measure of tissue viability; in no instance was this <10 μA/cm^2.

ΔIsc-tyr was expressed as a fraction of the maximal Isc response to catecholamines; the latter represented the combined responses to tyramine and epinephrine.

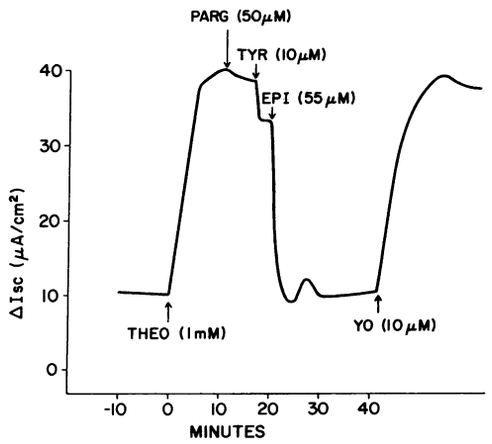

Figure 1. A representative tracing of Isc from the ileum of a CD rat. Tissues were stimulated to secrete with theophylline (THEO) before addition of the monoamine oxidase inhibitor pargyline (PARG) and tyramine (TYR). Epinephrine (EPI) was added immediately after the tyramine response. The cumulative Isc response to tyramine and epinephrine could be reversed with the alpha-2-adrenergic antagonist yohimbine (YO).

Table I. Profiles of Animal Groups

Group (*n*)	Body weight	Blood glucose	Gly-Hb
	g	*mg/100 ml*	%
AD			
Control (5)	234±15	98±5	5.3±0.15
AD, insulin-treated (6)	258±3	98±18	5.4±0.14
AD, untreated (5)	238±15	>400	7.0±0.23*
CD			
Control (6)	529±20	123±12	5.7±0.22
CD (6)	267±17	>400	10.4±1.1*

* $P < 0.01$. Values are mean±SEM for *n* rats. "Gly-Hb" refers to the percentage of circulating hemoglobin that is glycosylated.

Results

Animal groups. Three groups of diabetic rats were studied: two groups of AD rats (one receiving daily insulin injections, one not) and one group of CD rats. Littermates of each group served as controls. All untreated diabetic animals had persistent hyperglycemia (blood glucose > 400 mg/100 ml). The levels of glycosylated hemoglobin in each group are shown in Table I. No AD rats developed diarrhea, and there were no significant differences in body weight between AD rats and their littermates. CD rats failed to gain weight and, after 4–5 mo, all developed intermittent or persistent watery diarrhea. Stool and urine could not be separated for independent quantitation. Animals were given water ad lib. and did not appear dehydrated. Periodic measurements of blood urea nitrogen showed no difference from control rats. Mucosal histology from AD and CD groups was reviewed in a double blind manner by Dr. Robert Riddel (Department of Pathology, University of Chicago, IL), and no differences were observed in any of the above group with respect to villus length, crypt depth, light microscopic properties of enterocytes, number, and type of mesenchymal cells in the lamina propria, muscle mass, or blood vessels.

Intestinal fluid absorption in vivo. Ileal and colonic fluid absorptions were significantly less in CD rats than in their littermates (Table II). In fact, there appeared to be a net secretion of fluid by the ileum of CD rats. This was the case whether results are expressed as microliters per gram or as microliters per centimeter. Jejunal fluid absorption was not

Table II. In Vivo Intestinal Fluid Absorption in Diabetic, 6-OHDA-treated, and Control Rats

Group (*n*)	Fluid absorbed			Fluid absorbed		
	Jejunum	Ileum	Colon	Jejunum	Ileum	Colon
	μl/cm per h	*μl/cm per h*	*μl/cm per h*	*μl/g per h*	*μl/g per h*	*μl/g per h*
CD						
Control (6)	90±7	49±4	113±11	491±27	275±24	402±44
CD (6)	77±8	−3±3	52±10	434±30	−19±17	247±46
	NS	$P < 0.001$	$P < 0.001$	NS	$P < 0.001$	$P < 0.05$
AD						
Control (5)	96±8	53±9	100±10	777±51	420±89	449±30
AD-Ins (6)	77±17	49±5	103±13	640±66	465±63	394±59
AD (6)	93±14	49±5	116±9	744±55	434±65	578±72
	NS	NS	NS	NS	NS	NS
6-OHDA*						
6-OHDA (6)	64±8	8±6	64±8	433±31	0±20	253±43

Values shown are means±1 SEM for *n* animals. Locations of jejunal, ileal, and colonic loops are described under Methods. 2.0 ml HCO_3-Ringer solution was injected into loops at time zero. * Controls are those used with CD rats. AD-Ins, insulin-treated AD rats.

significantly altered. There were no significant differences in net fluid absorptions in jejunum, ileum, or colon between AD, insulin-treated AD, and control rats (Table II).

The effects on fluid absorption of chemical sympathectomy with 6-OHDA are shown in Table II. There were significant decreases in ileal and colonic but not jejunal fluid absorption in the 6-OHDA-treated animals. The observed pattern of altered fluid absorption was identical to that found in CD rats.

Isc measurements in vitro (Tables III and IV). Since Na, Cl, and HCO_3 transport responses to theophylline and epinephrine have been amply studied and correlate well with the oppositely directed Isc responses to these agents, in the present study we elected to follow Isc alone rather than attempt to measure changes in net fluxes of individual ions. Jejunal and ileal Isc responses to theophylline (1 mM) were the same in all groups (Table III). Effects of tyramine in CD rats are shown in Table IV. Although the ΔIsc-tyr was, on the average, smaller in jejunal mucosa from CD rats when compared with controls, this difference was not statistically significant. The Isc response to exogenously added epinephrine (ΔIsc-max) was significantly greater, however, in jejunum, suggesting denervation hypersensitivity. In ileal mucosa from CD rats, ΔIsc-tyr was significantly less than in controls, but no difference was noted in ΔIsc-max. To better relate the Isc responses to tyramine to the capacities of the tissues to respond to catecholamines, ΔIsc-tyr values were expressed as a fraction of ΔIsc-max. These ratios were significantly smaller in jejunum and ileum from CD rats, whereas no differences were noted in the corresponding values in AD rats and their controls (Table IV). Ileal and jejunal segments from 6-OHDA-treated rats gave similar Isc responses to tyramine and exogenously added epinephrine to those observed in CD rats.

Discussion

The above results suggest an explanation for the diarrhea that often develops in CD rats. The CD rats exhibited decreased rates of fluid and electrolyte absorption in the colon and ileum and diminished noradrenergic "tone" in their intestinal mucosa. Adrenergic innervation has been shown to play a major role in the regulation of fluid and electrolyte transport in the intestinal tract. Impairment of adrenergic regulatory mechanisms can alter the homeostatic balance of intestinal ion transport to favor secretion. In previous studies, patients who had undergone bilateral sympathectomy for hypertension often developed persistent and distressing diarrhea (13). Similarly, surgical sympathectomy in dogs (14) and chemical sympathectomy with 6-OHDA in rabbits (Tapper, E. J., personal communication) both cause diarrhea. In vitro stimulation by epinephrine or norepinephrine of alpha-2 receptors on rabbit ileal enterocytes stimulates active absorption of Na and Cl and inhibits active secretion of Cl and HCO_3 (7, 8, 15). These effects have been shown by Tapper et al. (11) to also occur when norepinephrine is released from endogenous stores in rabbit ileal mucosa by tyramine. Using [^{3}H]norepinephrine, Wu and Gaginella (16) demonstrated the presence in rat

Table III. Isc Responses to Theophylline (1 mM) in Diabetic and Control Rats

Group (*n*)	Jejunum Isc	Ileum Isc
	μA/cm²	*μA/cm²*
CD		
Control (8)	20±1.2	44±4.2
CD (6)	25±3.0	39±6.3
	NS	NS
AD		
Control (5)	32±1.9	47±5.1
AD (5)	35±3.2	42±2.5
	NS	NS

Values are mean±1 SEM for *n* rats.

Table IV. ΔIsc-tyr Alone and Tyramine plus Epinephrine (ΔIsc-max) in Diabetic and Control Rats

	Jejunum			Ileum		
Group (*n*)	ΔIsc-tyr	ΔIsc-max	*R*	ΔIsc-tyr	ΔIsc-max	*R*
	$\mu A/cm^2$	$\mu A/cm^2$	%	$\mu A/cm^2$	$\mu A/cm^2$	%
CD						
Control (8)	16±1.7	19±1.7	85±2.5	29±2.1	37±3.3	79±2.6
CD (6)	11±1.4	28±3.0	43±6.0	19±4.2	42±8.6	47±6.1
	NS	$P < 0.05$	$P < 0.001$	$P < 0.05$	NS	$P < 0.001$
AD						
Control (5)	24±1.5	33±2.3	72±1.4	27±2.0	34±5.3	74±5.2
AD (5)	26±2.1	40±4.7	70±4.6	31±3.7	40±4.7	77±1.0
	NS	NS	NS	NS	NS	NS

Values are mean±SEM for *n* rats. ΔIsc-tyr is the decrease in Isc caused by serosal addition of tyramine (10 μmol/liter) in the presence of pargyline (50 μM). ΔIsc-max is the accumulative decrease in Isc caused by the sequential additions of tyramine and then epinephrine (5.5 μmol/liter). *R*, ΔIsc-tyr/ΔIsc-max × 100.

colonic mucosa of a functional noradrenergic neural network closely associated with the epithelium.

Autonomic neuropathy and, in particular, adrenergic neuropathy has been shown to develop as a chronic complication of diabetes. Hensley and Soergel (17) reported lesions of the dendritic processes of the pre- and paravertebral sympathetic ganglia. Low et al. (18) performed quantitative histological studies of greater splanchnic nerves removed at autopsy from patients with diabetic neuropathy; they found significant reductions in fiber density and segmental demyelination of teased fiber preparations. Similarly, Schmidt et al. (19) demonstrated in rats made chronically diabetic with streptozocin that there is both histological evidence of visceral nerve destruction and biochemical evidence of cholinergic as well as adrenergic denervation (decreased choline acetyltransferase and dopamine β-hydroxylase activity, respectively). More recently, studies by Lincoln et al. (20) of the myenteric plexus in streptozocin-treated rats suggest selective destruction of adrenergic nerves (20). The present studies are consistent with these observations. Nondiabetic animals partially sympathectomized with 6-OHDA demonstrated a significant decrease in intestinal fluid absorption similar in distribution and magnitude to the pattern seen in CD rats. The tyramine-releasable pool of norepinephrine was decreased in mucosal preparations from CD, but not AD rats. Tissue responsiveness to exogenously added epinephrine was not affected, however. The small increase in Isc response to exogenously added epinephrine in the jejunum may have been a consequence of receptor denervation hypersensitivity (21).

It is of interest that jejunal fluid absorption in CD rats was not significantly different from that of control animals, even though endogenous norepinephrine stores were reduced. Because jejunal fluid absorption also remained normal in rats treated with 6-OHDA, it is likely that the adrenergic nervous system plays less of a role in regulating fluid and electrolyte transport in jejunum than it does in colon and ileum. The fact that epinephrine elicited smaller decreases in Isc in jejunum than in colon and ileum is consistent with this possibility.

Diminished fluid and electrolyte absorption in the ileum and colon of CD rats could also be a consequence of impaired enterocyte transport function caused by the metabolic disturbances associated with the diabetic state or by streptozocin. Contrary to the latter possibility is the observation that intestinal fluid absorption was normal in AD rats. Contrary to the former possibility is the observation that in vitro responsiveness to both exogenously added epinephrine and theophylline remained normal in the CD rats, indicating that diabetes does not alter the maximal capacities of the absorptive and secretory systems for ions. Although CD rats weighed substantially less than their littermate controls, this form of malnutrition does not appear to diminish the absorption of nutrients and other ions. For example, ileal SO_4 absorption is the same in CD and control rats (22), *l*-alanine absorption is actually enhanced in the ileum of CD rats, and D-glucose absorption is increased in both ileum and jejunum of CD rats (22, 23).

Whether diarrhea in humans with long-standing diabetes can be explained by a similar pathophysiological mechanism, i.e., by decreased ileal and colonic mucosal fluid and electrolyte absorption, remains to be proved. Whalen et al. (24), using the triple lumen tube perfusion technique, found that jejunal and ileal water and electrolyte absorption in diabetic patients with diarrhea was not abnormal. The group of patients they studied varied greatly, however, in the severity of their diarrhea (ranging from 211 to 1,605 g/d), and there is no indication of how many of the patients were close to the lower end of this range. The inherent variability of intestinal tube perfusion studies may also have contributed to their failure to detect abnormal fluid absorption.

The CD rats in our study uniformly developed diarrhea after 4–6 mo, whereas, clinically, diabetic patients with diarrhea frequently experience alternating periods of diarrhea and constipation. This difference may be attributable to the fact that CD rats had severe uncontrolled diabetes for prolonged periods, a circumstance rarely encountered in a patient population. Patients with diabetic enteropathy may compose a more heterogeneous group; that is, they may have varying degrees of impairment of adrenergic or cholinergic innervation. Therefore, as also suggested by others (25), gut function may depend

in part on the dominant regulatory mechanism at that particular point in time. Intractable diarrhea suggests a predominantly adrenergic rather than cholinergic neuropathy.

Based on the findings of this study, we treated empirically three diabetic patients with diarrhea (500–1,500 ml/d) with the alpha-2-adrenergic agonist clonidine (26). In each of these patients, stool volume and stool frequency were substantially reduced by clonidine. Additional studies are needed to properly evaluate the efficacy of this mode of treatment and its implications for the etiology of the diarrhea. In particular, we need to examine the value of clonidine in other forms of chronic diarrhea. Whether the efficacy of clonidine in these diabetic patients was due solely to its enhancement of fluid absorption, or whether enhancement of anal sphincter tone or a decrease in motility may also have played a role is uncertain and remains to be investigated.

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