The short-circuit current of the ileum, but not the colon, is altered in the streptozotocin diabetic rat

Abigail Forrest, Rajesh Makwana, and Mike Parsons

Abstract: Ion transport in control and streptozotocin-diabetic rat colon and ileum was studied using the Ussing chamber technique. No differences were observed between control and diabetic colonic mucosal short-circuit current under either basal or carbachol (100 nmol/L – 1 μmol/L)-stimulated or prostaglandin E_2 (100 nmol/L – 1 μmol/L)-stimulated conditions. Similarly to colonic tissues, no differences in the short circuit current in either carbachol-stimulated or prostaglandin E_2-stimulated tissues were observed between control and diabetic ileal mucosa. The basal diabetic ileal short circuit current (99.58 ± 22.67 μA) was significantly greater than that of control ileal tissues (29.67 ± 4.45 μA). This difference was abolished by the sodium–glucose-cotransporter inhibitor, phloridzin (50 μmol/L) (118.00 ± 28.09 μA vs. 25.60 ± 4.59 μA) and was also prevented by the replacement of glucose with mannitol in the buffer bathing the apical side of the tissue (control: 17.05 ± 5.85 μA vs. 17.90 ± 3.10 μA). Acetazolamide (450 μmol/L; a carbonic anhydrase inhibitor), amiloride, and bumetanide (100 μmol/L each; Na^+-channel blockers), piroxicam (50 μmol/L; a COX_1 cyclooxygenase inhibitor), and ouabain (1 mmol/L; a K^+ transport inhibitor) had no effect on the basal short circuit current of either control or diabetic ileal tissues. This indicated that the alteration in the basal short circuit current of diabetic ileal tissues was due to a change in cellular glucose transport, whereas the evoked changes in short circuit current were unaffected by the diabetic state.

Key words: diabetes, gastrointestinal tract, secretion, short circuit current.

Résumé : On a examiné le transport ionique dans l'iléon et le côlon de rats témoins et de rats rendus diabétiques par la streptozotocine en utilisant la méthode des chambres de Ussing. Aucune différence n'a été observée entre le courant de court circuit (CCC) de la muqueuse colique des rats diabétiques et témoins, que ce soit dans des conditions basales, stimulées par le carbachol (100 nmol/L – 1 μmol/L) ou stimulées par la prostaglandine E_2 (100 nmol/L – 1 μmol/L). Aucune différence n'a été relevée non plus dans le courant de court-circuit des tissus stimulés par le carbachol ou la prostaglandine dans la muqueuse iléale des rats témoins et diabétiques. Le courant de court-circuit iléal diabétique basal (99,58 ± 22,67 μA) a été significativement plus élevé que celui des tissus iléaux témoins (29,67 ± 4,45 μA). Cette différence a été supprimée par la phloridzine (50 μmol/L), un inhibiteur du cotransport sodium-glucose, (118,00 ± 28,09 μA vs. 25,60 ± 4,59 μA) et prévenue en remplaçant le glucose par du mannitol dans la solution tampon baignant le côté apical du tissu (témoin : 17,05 ± 5,85 μA vs. 17,90 ± 3,10 μA). L'acétazolamide (450 μmol/L; un inhibiteur de l'anhydrase carbonique), l'amiloride et le buténamide (100 μmol/L chacun; des bloqueurs des canaux Na^+), le piroxicam (50 μmol/L; un inhibiteur de la cyclooxygénase COX_1), et l'ouabaïne (1 mmol/L; un inhibiteur du transport de K^+) n'ont pas eu d'effet sur le CCC basal des tissus iléaux diabétiques et témoins. Ces résultats indiquent que la modification observée dans le courant de court circuit basal des tissus iléaux diabétiques a été causée par une modification du transport de glucose cellulaire, alors que les changements induits dans le courant de court circuit n'ont pas été influencés par l'état diabétique.

Mots clés : diabète, tube digestif, sécrétion, courant de court circuit.

[Traduit par la Rédaction]

Introduction

Diabetes mellitus is associated with a range of chronic complications and 45% of diabetic patients suffer from gastrointestinal symptoms (Quigley 1997). Those symptoms associated with the lower gastrointestinal tract commonly manifest themselves as changes in propulsion leading to diarrhea and (or) constipation (Malins and French 1957; Katz and Spiro 1966; Maxton and Whorwell 1991; Haines 1995)

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Whereas altered gastrointestinal function in diabetes is well established, there is debate about the mechanisms underlying these changes. Numerous studies have investigated the role of gastrointestinal motility alterations in the development of these symptoms, whereas in comparison, relatively little has been done to investigate changes in intestinal absorption and secretion that may occur in the diabetic state.

Only a small amount of work has been performed to assess the role of altered ion transport in the development of diabetic gastrointestinal complications. Perdue and Davison (1988) used the Ussing chamber technique to measure the short-circuit current (SSC) of 8-week diabetic rat ileum tissues. Although the thickness of the mucosa was found to be significantly greater in diabetic animals compared with controls, no difference in either the basal SCC, or urecholine-stimulated SCC, was recorded. However, when the conductance of the tissue was calculated, it was found to be signifi-

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cantly lower in the diabetic tissue, suggesting that the resistance of the tissue was higher.

Chang et al. (1985) measured the SCC in acute (1 week)- and chronic (4–6 months)-treated diabetic rat ileum. They found that the increase in SCC in response to a theophylline (a phosphodiesterase inhibitor) was not different in diabetic tissues compared with controls. However the inhibitory effect of tyramine (which causes the release of endogenous noradrenaline) on theophylline-stimulated SCC was less in the diabetic ileum. Furthermore, in vivo studies on the measurement of intestinal fluid absorption demonstrated that there was a significant reduction in the fluid absorption measured in chronically diabetic ileum and colon compared with that observed in control rats, although acutely diabetic rats showed no signs of change.

The aim of this study is to further investigate possible changes in ion movement in diabetic colon and ileum that may be responsible for diabetic gastrointestinal complications such as constipation and diarrhea.

Methods

Male Wistar rats (250–350 g) were injected with streptozotocin (STZ; 65 $mg \cdot kg^{-1}$; 1 mL/100 g body mass, i.p.), or the equivalent volume of citrate buffer (0.9% NaCl + citric acid, pH 4.5), i.p. The mass and blood glucose level of each rat was measured and recorded, and the rats were placed in cages (1 control rat and 1 STZ-treated rat per cage) The rats were given 2% sucrose to drink for 2 days after STZ injection to prevent the effects of acute hypoglycaemia and then given access to food and water ad libitum, until sacrifice. Rats were sacrificed by carbon dioxide (CO_2) overdose 8 weeks after injection. Housing conditions and all experimental work were conducted in accordance with the Animals (Scientific Procedures) Act 1986 under Project Licence Number PPL 70 4649 with a Project Title of Gastrointestinal Research.

The ileum and colon were removed and immediately immersed in Krebs buffer (118.3 mmol NaCl/L; 4.7 mmol KCl/L; 1.2 mmol $MgSO_4$/L; 1.2 mmol KH_2PO_4/L; 25 mmol $NaHCO_3$/L; 11.1 mmol glucose/L; 2.5 mmol $CaCl_2$/L) maintained at 37 °C and gassed with 95% O_2 : 5% CO_2.

Ion transport across the colonic and ileal epithelia was measured as an SCC of voltage-clamped tissues using the Ussing chamber apparatus. Blunt dissection of the rat colon and ileum was performed such that the whole tissues were cut open and the contents removed. The tissue was pinned onto a board (muscle side up) and the muscle layers peeled away from the epithelium with the aid of fine forceps. The epithelium was then stretched out and placed over the window of the Ussing chamber (window area = 0.63 cm^2). The tissue was voltage clamped to 0, with an imposed break of 2 mV every 30 s to allow the calculation of resistance according to Ohm's law: $V/I = R$. The tissue was allowed to equilibrate for approximately 30 min after setting up before experimental protocols were commenced. Drugs were added to either the apical (A), basolateral (B), or both (AB) sides of the tissue as appropriate.

Concentration-effect curves to carbachol and PGE_2 were performed on the colonic preparations, and the effect of each concentration expressed as the change in SCC from basal values (Δ SCC (μA)). Two-way ANOVA followed by the Bonferroni modified *t* test for multiple comparisons was used to test for statistical significance between concentration-effect curves performed on control and diabetic colon preparations, whereas Student's *t* test for unpaired data was used to compare basal control and diabetic tissue short circuit currents.

The effects of single concentrations of carbachol, PGE_2, tetrodotoxin, acetazolamide, piroxicam, bumetanide, piretanide, amiloride, and phloridzin were studied on the rat distal ileum. Drugs were added to the apical or basolateral, or both sides of the tissue as appropriate. The responses to carbachol and PGE_2 were expressed as the change in SCC from basal values (Δ SCC (μA)). Other drug responses were expressed as absolute SCC only. Student's *t* test for paired data was used to test for significance between the pre- and post-drug values for single concentrations of drugs for both control and diabetic responses, whereas Student's *t* test for paired data was used to test between values expressed as a change in SCC.

Further studies were performed in the absence of apical glucose to assess the role of glucose in the generation of the SCC of the rat distal ileum epithelium. Experiments were performed as described previously, but the tissues were bathed in a glucose-free buffer instead of standard Krebs–Heinseleit buffer on the apical side (glucose replaced with mannitol in a 1 mmol/L: 1 mmol/L ratio), whereas the basolateral side was bathed with standard Krebs–Heinseleit buffer. Data was expressed in μA for both control and STZ-diabetic tissues, and Student's *t* test for unpaired data was used to test for significance between the control and diabetic short circuit currents. All graphs represent the mean of 'n' tissues ± SE.

All drugs were obtained from Sigma UK (Poole, Dorset), with the exception of piretanide, a gift from Dr H. Cox, originally from Hoechst. Solvents for the drugs were as follows: amiloride, tetrodotoxin, PGE_2, and carbachol were dissolved in distilled water; bumetanide and phloridzin were dissolved in ethanol; piroxicam was dissolved in DMSO; acetazolamide was dissolved in 1 mol/L ammonium hydroxide, and piretanide was dissolved in distilled water with 1 drop of concentrated sodium hydroxide.

Results

Male rats were injected with STZ (65 $mg \cdot kg^{-1}$) or citrate buffer. Diabetes was considered to be established by a blood glucose level of ≥ 200 $mg \cdot dL^{-1}$ (Talubmook et al. 2003). The STZ injection generally rendered rats diabetic within 1 week, as judged by the onset of polydipsia and polyuria, whereas the citrate buffer had no effect. Rats were used after 8 weeks at which point the mean blood glucose levels were 106.10 ± 0.11 $mg \cdot dL^{-1}$ (control) and 517.47 ± 0.74 $mg \cdot dL^{-1}$ (STZ).

Colon

The basal short circuit current of the colonic epithelium did not significantly differ between control and diabetic tissues ($n = 8$; 32.51 ± 4.88 μA (control) vs. 27.23 ± 3.29 μA (STZ).

The tissue resistance was calculated using a rearrangement of the formula '$V = IR$', where I is the short circuit

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current of the tissue, and V is the 2 mV voltage spike. In the colon, the calculated resistance of the diabetic epithelium was not significantly different to that of the control tissues ($n = 8$ for both; 97.82 ± 6.19 $\Omega \cdot cm^{-2}$ (control) vs. 116.78 ± 11.29 $\Omega \cdot cm^{-2}$ (STZ)).

The effects of carbachol and prostaglandin E_2

Cumulative concentration-effect curves to carbachol were performed on both control and diabetic colonic epithelium, and the effect on the SCC recorded. The response to carbachol (B), where B is basolaterally, did not significantly differ between control ($n = 9$) and diabetic ($n = 6$) tissue at any concentration used (100 nmol/L: 14.89 ± 4.22 µA (control) vs. 10.01 ± 4.47 µA (STZ); 300 nmol/L: 17.4 ± 6.63 µA (control) vs. 9.03 ± 4.04 µA (STZ); 1 µmol/L: 125.33 ± 16.45 µA (contorl) vs. 116.50 ± 25.44 µA (STZ), $p > 0.05$). The increase in the SCC from the basal values that was produced by carbachol (1 µmol/L) was significant in both control and diabetic tissues.

Cumulative concentration-effect curves to prostaglandin E_2 (B) were also performed on both control and diabetic colonic epithelium, and the effect on the SCC again recorded. The response to prostaglandin E_2 did not significantly differ ($p > 0.05$) between control ($n = 6$) and diabetic ($n = 5$) tissue at any concentration (100 nmol/L: 15.50 ± 9.54 µA (control) vs. 20.40 ± 8.07 µA (STZ); 300 nmol/L: 17.00 ± 13.39 µA (control) vs. 29.28 ± 10.64 µA (STZ); 1 µmol/L: 17.50 ± 12.09 µA (control) vs. 42.40 ± 16.22 µA (STZ)).

Ileum

The basal SCC of the diabetic ileal epithelium ($n = 8$) was significantly ($p < 0.01$) greater than that measured for control tissues ($n = 9$; 29.67 ± 4.45 µA (control) vs. 99.58 ± 22.67 µA (STZ); Fig. 1*a*). Experiments performed on the ileal tissue taken from STZ-injected, nondiabetic rats confirmed that this increased basal SCC was an effect of the diabetic state and not a general toxic effect of the STZ injection ($n = 8$; 11.52 ± 2.32 µA (control) vs. 11.72 ± 0.62 µA (STZ); Fig. 1*c*).

The resistance of the diabetic tissue was significantly lower than that calculated for the control preparations ($n = 5$; 107.18 ± 15.74 $\Omega \cdot cm^{-2}$ (control) vs. 31.93 ± 1.84 $\Omega \cdot cm^{-2}$ (STZ); Fig. 1*b*). Again, similarly to the SCC, the tissue resistance was not significantly changed from control values in the ilea taken from STZ-injected, nondiabetic rats ($n = 8$; 276.04 ± 42.24 mΩ (control) vs. 271.33 ± 15.43 mΩ (STZ); Fig. 1*d*).

The effects of carbachol and prostaglandin E_2

Carbachol (10 µmol/L; (B)) produced an increase in SCC in both control ($n = 8$) and diabetic ($n = 9$) rat ileum. The data were expressed as a change in SCC (from basal values), and no difference in response between control and diabetic tissues were observed (102.41 ± 10.76 µA (control) vs. 71.94 ± 10.89 µA (STZ); $p > 0.05$).

Similarly to carbachol, prostaglandin E_2 (10 µmol/L; (B)) also produced an increase in SCC in both control ($n = 8$) and diabetic ($n = 9$) rat ileum. The data were expressed as a change in SCC (from basal values), and there was no difference in the response of diabetic tissue compared with control tissue (21.68 ± 2.94 µA (control) vs. 19.41 ± 3.26 µA (STZ); $p > 0.05$).

The effects of tetrodotoxin on control and diabetic rat ileum basal SCC

Tetrodotoxin (1 µmol/L; (B) had no effect on either control or diabetic SCC ($n = 5$; data not shown).

The effects of acetazolamide, piroxicam, bumetanide, amiloride, ouabain and piretanide on control and diabetic rat ileum basal SCC

The sequential addition to the Ussing chamber of the carbonic anhydrase inhibitor, acetazolamide (450 µmol/L; (AB)); the COX_1 cyclooxygenase inhibitor, piroxicam (50 µmol/L; (AB)); and the $Na^+K^+Cl^-$-cotransporter inhibitor, bumetanide (100 µmol/L; (B)) had no effect on the SCC of either control or diabetic rat ileum epithelium (Fig. 2*a*; $p > 0.05$; $n = 6$). Similarly, single concentrations of the Na^+-channel blocker, amiloride (100 µmol/L; (A); $n = 6$; Fig. 2*b*); and the K^+ transport inhibitor, ouabain (1 mmol/L; (B); $n = 4$; Fig. 2*c*) had no effects on the SCC of either control or diabetic rat ileum epithelium. The lack of effect of bumetanide was confirmed by the use of piretanide in a single experiment (200 µmol/L; (B); $n = 1$; Fig. 2*d*).

The effect of phloridzin

Apical application of the Na^+/Glucose cotransporter inhibitor, phloridzin (50 µmol/L), reduced the SCC of the diabetic tissue to levels similar to that of the control tissues, whereas the SCC of the control tissues was not significantly affected by phloridzin (31.20 ± 14.78 µA vs. 25.15 ± 13.33 µA (control); 118.00 ± 28.09 µA vs. 25.60 ± 4.59 µA (STZ); $p < 0.05$; $n = 5$; Fig. 3*a* and 3*b*). Basolateral application of phloridzin also produced a reduction in the SCC of both control and diabetic ileum preparations (26.06 ± 9.26 µA vs. 16.56 ± 4.96 µA (control); 138.00 ± 69.70 µA vs. 62.86 ± 34.94 µA (STZ); $p < 0.05$; $n = 4$). When the responses to apically and basolaterally applied phloridzin were expressed as percent inhibition and compared, the control responses were not significantly different from each other, whereas the diabetic response was significantly smaller ($p < 0.05$) after basolaterally applied phloridzin than that observed after apical application (23.00% ± 6.58% vs. 30.48% ± 10.92% (control); 76.19% ± 11.89% vs. 57.13% ± 1.75% (STZ)). The response of both control and diabetic tissues to apical application was immediate, whereas the response to basolateral application was delayed by approximately 1 min. Furthermore, the time taken to reach maximum inhibition was greater when phloridzin had been applied basolaterally for both control (10.5 min (basolateral) vs. 5.6 min (apical)) and diabetic (13.5 min (basolateral) vs. 7.5 min (apical)) preparations.

Incubation with mannitol

Tissues were set up as above, and the basolateral side was bathed in standard Krebs buffer, whereas the apical side of the tissue was bathed in a glucose-free buffer Incubation of the apical side of the tissue with a glucose-free buffer produced SCC that were similar to those recorded in the presence of phloridzin (mannitol: 17.05 ± 5.85 µA (control) vs. 17.90 ± 3.10 µA (STZ); $n = 5$; Fig. 3*c*; phloridzin: 25.15 ±

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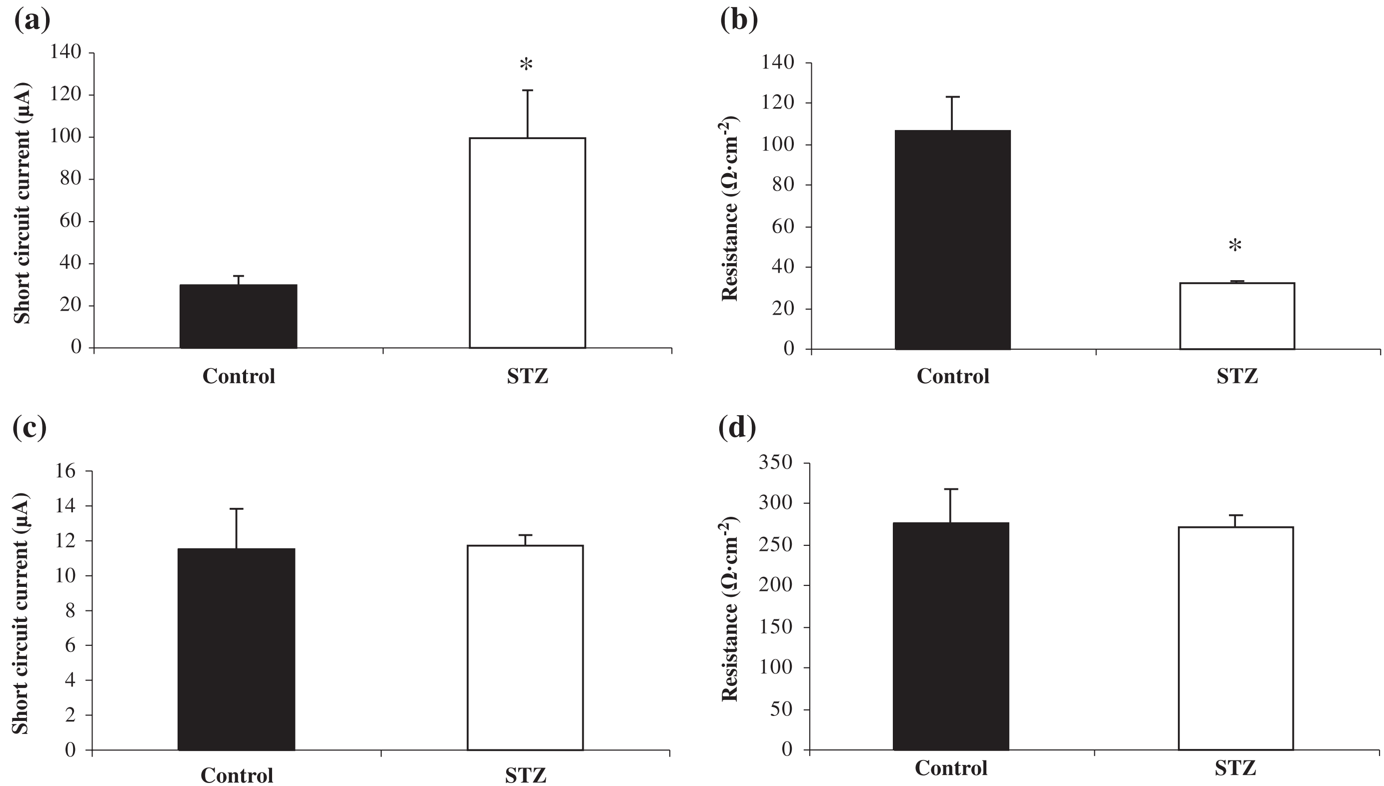
Fig. 1. A comparison of the (*a*) basal short circuit current and (*b*) resistance of control (■) and diabetic (□) rat ileal epithelium (n = 8), and of the (*c*) basal short circuit current and (*d*) resistance of control (■) and STZ-injected-non-diabetic (■) rat ileal epithelium (n = 3; mean ± SE). *, $p < 0.05$ vs. control values. Resistance is expressed in mΩ, as calculated from the basal short circuit current and imposed break of the voltage clamp (2 mV every 30 s) using a rearrangement of the formula $V = IR$.



13.33 μA (control) vs. 25.60 ± 4.59 μA (STZ); $p < 0.05$; n = 5; Fig. 3*b*). In the presence of mannitol, the resistance of the diabetic tissues was not significantly different compared with that of the controls (33.14 ± 4.23 mΩ (control) vs. 35.83 ± 4.55 mΩ (STZ); n = 5). Compared with the resistance measured in the tissues bathed in glucose-containing buffer, the control resistance was not significantly different (33.14 ± 4.23 mΩ (mannitol) vs. 58.25 ± 15.74 mΩ (glucose); $p > 0.05$). However, the resistance of the diabetic tissues bathed in mannitol-containing buffer was significantly greater ($p < 0.05$) than that measured in tissues bathed in glucose-containing buffer (35.83 ± 4.55 mΩ (mannitol) vs. 14.56 ± 1.84 mΩ (glucose)). Responses to carbachol were used as an internal control and were reduced in tissue bathed with mannitol compared with those bathed with glucose (104.63 ± 20.38 μA vs. 132.10 ± 13.02 μA (control); 71.44 ± 13.78 μA vs. 171.52 ± 28.79 μA (STZ)).

Discussion

It has been well established that there are alterations in gastrointestinal motility in the diabetic state. However, less well documented are changes in gastrointestinal secretion and absorption, which may also account for complications such as diarrhea that is seen in diabetic patients (Valdovinos et al. 1993). Studies were performed on tissues taken from animals 8 weeks after STZ administration since this was the time that consistent changes in gastrointestinal function have been observed (Talubmook 2002).

In both the colon and the ileum, carbachol and PGE_2 induced increased ion movement, measured as an increase in SCC. In both tissue preparations, no significant differences between control and diabetic response were observed in response to either carbachol or PGE_2. It therefore appears that diabetes does not have an effect on the ability of tissues to respond to stimulant drugs.

In the present study, the basal SCC of the diabetic colonic tissues was unaltered and there was no change in the resistance of the tissues. However, experiments performed in the ileum demonstrated that there was a significantly higher basal SCC in diabetic tissues compared with controls. In addition, the resistance of the diabetic ileal tissues was significantly lower, indicating that the permeability of the tissue was greater (e.g., the tissue was leakier). A study by Meddings et al. (1999) with experiments using sucrose as a marker of altered intestinal permeability in spontaneously diabetic BB rats showed that there is a significant increase in the permeability of the diabetic small intestine after a life-span of 50 days, whereas colonic permeability was unchanged.

Therefore, in an attempt to characterize the nature of the increased SCC, the effect of a number of pharmacological tools was studied. Acetazolamide (a carbonic anhydrase inhibitor), amiloride (a Na^+-channel blocker), piroxicam (a COX_1 cyclooxygenase inhibitor), and ouabain (a K^+ transport inhibitor) had no effect on the SCC of either control or diabetic tissues. Bumetanide and piretanide ($Na^+K^+Cl^-$ cotransporter inhibitors) also had no effect on the SCC.

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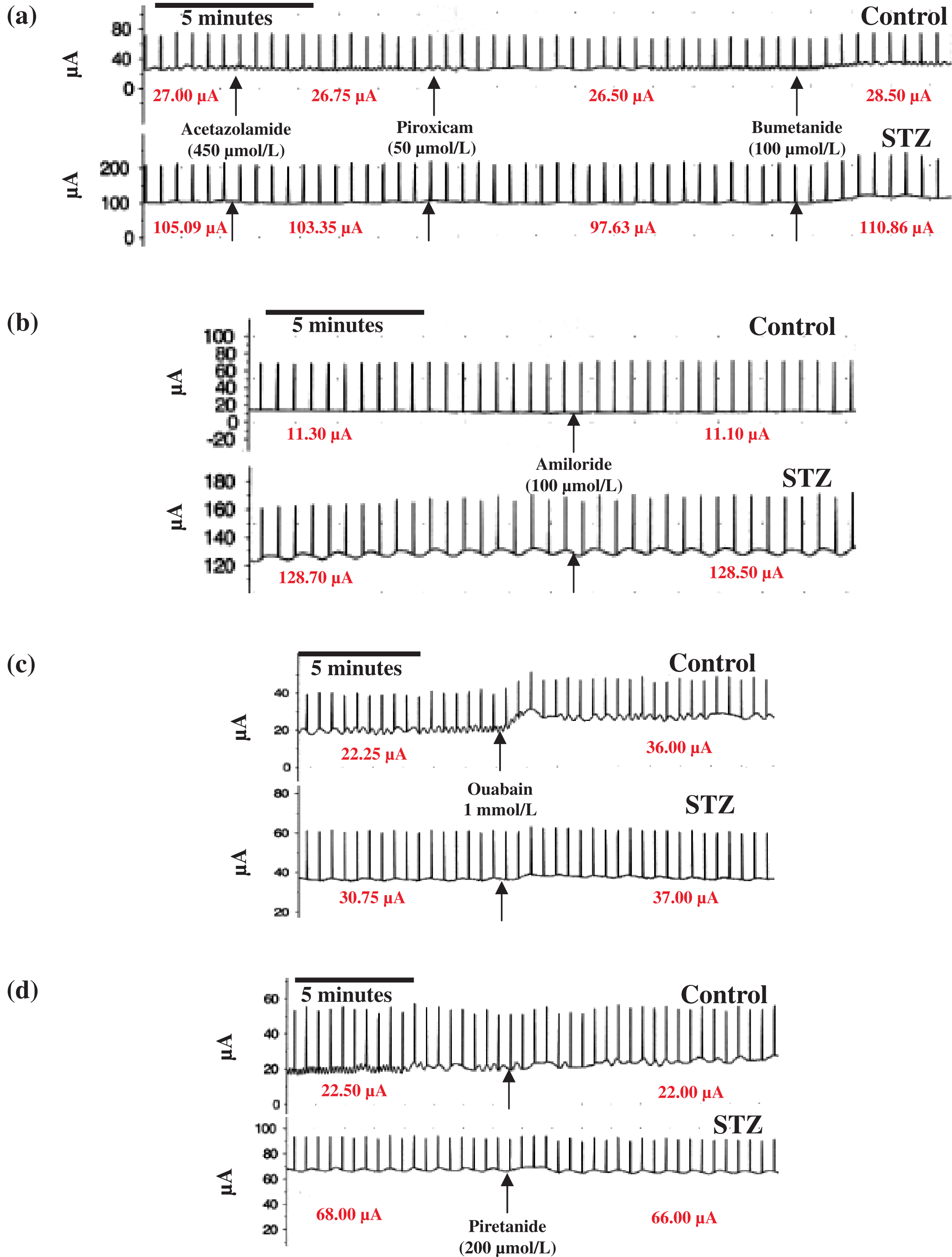
Fig. 2. Experimental traces to illustrate that (*a*) sequential addition of acetazolamide (450 µmol/L), piroxicam (50 µmol/L), and bumetanide (100 µmol/L; n = 6), (*b*) amiloride (100 µmol/L; n = 6), (*c*) ouabain (1 mmol/L; n = 4), and (*d*) piretanide (200 µmol/L; n = 1) had no significant effect on basal short circuit current in control and diabetic rat ileum. Absolute short circuit current values on the traces, pre- and post-treatment, are expressed in µA.



Little work has been reported investigating the effects of these compounds on the basal SCC of either the ileum or colon, particularly with regard to diabetes. Fedorak et al. (1991*a*) used the Ussing chamber technique to investigate the effect of ouabain on 7- and 90-day STZ-diabetic rat ileum. In both control and diabetic tissues, the SCC developed in response to exogenously applied glucose was inhibited by ouabain. This inhibition was significantly smaller in

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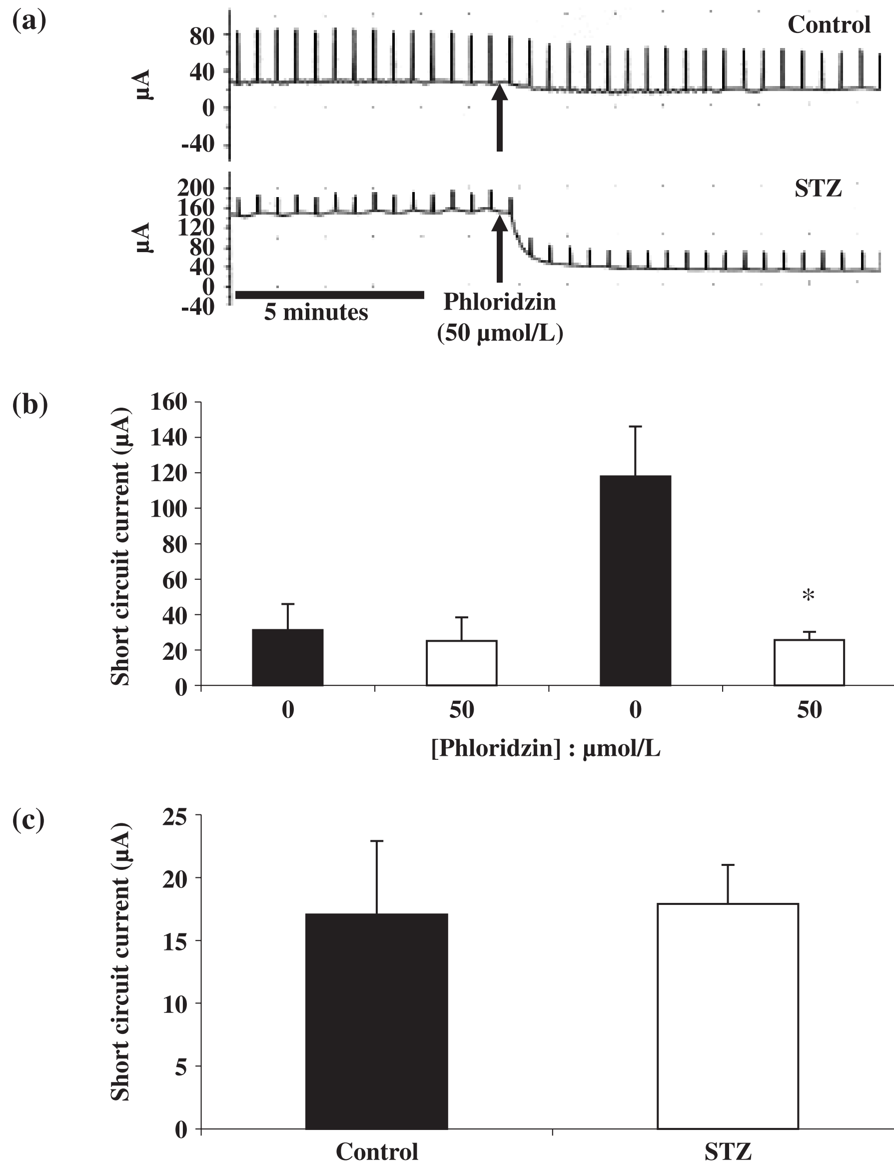
Fig. 3. The effect of phloridzin (50 μmol/L) on the basal short circuit current shown by (*a*) experimental trace and (*b*) absolute short circuit current (μA). (*c*) The effect of bathing the apical side of tissues in glucose-free buffer on short circuit current, in control (■) and diabetic (□) rat ileum (mean ± SE, $n = 5$). *, $p < 0.05$ vs. pre-treatment value.



diabetic tissues compared with controls, indicating that the diabetic ileum is less sensitive to ouabain.

In the present study, the apical application of phloridzin, the Na^+/glucose cotransporter inhibitor (which competes with glucose for binding to the transporter, but is not transported itself (Fedorak et al. 1989)) had no significant effect on the control ileal SCC, whereas the SCC of the diabetic tissues was reduced to near-control values. Control experiments were performed by applying phloridzin to the basolateral side of the tissue. Again, in control tissues, no significant effect was observed, whereas in diabetic tissue, the effect was similar to that observed in the presence of apical phloridzin. However, the onset of the SCC reduction was delayed by approximately 1 min and the length of time taken for the maximum inhibition to be achieved was longer than that observed in the presence of apically applied phloridzin, indicating that the compound might have moved through the tissue via the tight junctions. An explanation for why the colonic SCC was not observed to be greater in diabetic tissues and was unaffected by phloridzin is the absence of the sodium–glucose co-transporter (SGLT-1) in this area of the gut (Shirazi-Beechey, personal communication 2004).

Replacing glucose with mannitol in the apical chamber reduced the SCC of the diabetic tissues down to levels similar to those of the controls. This supported the phloridzin experiments by indicating that it was an alteration in the Na^+/glucose cotransporter that was responsible for the increased SCC.

A number of reports have been made regarding the transport of glucose by SGLT-1. Dyer et al. (2003*b*) suggested that glucose in the small intestine is detected by a glucose sensor present on the luminal membrane of enterocytes, and that glucose binds to this sensor generating an intracellular

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signal and leading to the enhancement of SGLT-1 expression. In addition to this, perfusion of the sheep small intestine with an increased glucose medium upregulated SGLT-1 abundance (Dyer et al. 2003*a*). In diabetes, there is an increase in the capacity of the small intestine to absorb glucose (Fedorak et al. 1991*b*; Dyer et al. 1997), and in streptozotocin diabetic rats, using the Western blotting studies, the small intestine shows an increase in the abundance of SGLT-1 after a 4-week duration of diabetes (Dyer et al. 1997).

Levine et al. (1982) demonstrated in nondiabetic rats that plasma-to-lumen movement of glucose in vivo in the ileum was proportional to blood glucose concentration. In addition, plasma volume expansion by the perfusion of 10% dextran increased the level of glucose secretion, indicating that glucose secretion is a passive process. Moreover, in 3–4 week STZ-diabetic rats, glucose secretion was considerably higher than in control rats.

These experiments are supported by a number of others. Thomson (1981) showed that the radiolabelled ^{14}C-glucose uptake was significantly increased in both STZ- and alloxan-diabetic jejunum and ileum from 3-days diabetes and longer. This increase in glucose uptake became more pronounced with increasing duration of diabetes. Experiments performed by Fedorak et al. (1991*b*) in the ileum taken from 90 day, STZ-diabetic rats measured the maximal transport capacity and the carrier affinity for 3-O-methyl-D-glycopyranose (3-OMG; a non-metabolized analogue of D-glucose using the sodium-dependent glucose cotransporter for mucosal transport). The maximal transport capacity was increased in diabetic tissues compared with controls by 30-days duration of diabetes, and further increased by 60- and 90-days duration. This data suggests that an adaptive process occurs to account for increased glucose availability in the diabetic state, although experiments performed on control-fed rats demonstrated similar results indicating that these adaptations are independent of hyperphagia (Fedorak et al. 1991*b*). In 120-day STZ-diabetic rat ileum, a phloridzin-sensitive 5-fold increase in 3-OMG flux was seen, with phloridzin blocking both the control and diabetic net 3-OMG flux. No change in the affinity for the carriers was observed, but the ^{3}H-phloridzin binding was greater in diabetic tissues, indicating an increase in the number of Na^{+}-dependent glucose carriers.

In summary, evoked ion transport is not altered by the diabetic state, but there is an increase in the basal diabetic ileal SCC. This increase is related to the Na^{+}/glucose co-transporter, and may be due to increased numbers or activity of this transporter.

Acknowledgements

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