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The mechanism by which interleukin-1 beta reduces net fluid absorption from the rat colon



Abstract

IL-1beta is suspected to be involved in the diarrhea that always accompanies inflammatory bowel disease. This work was aimed at studying the in vivo effect of IL-1beta on the net absorption of fluid, Na⁺ and Cl⁻ from the rat colon, and at delineating its mechanism of action. Rats were injected i.p. with IL-1beta (1 mug/kg body weight) and the colon was perfused, four hours later, with Krebs-Ringer buffer. Net fluid absorption was calculated as the difference between the total volume of the buffer infused and collected per cm² of perfused intestine.

Chloride in both buffers was determined by titration according to Mohr's method and net Cl⁻ absorption was calculated in the same way. IL-1beta reduced the net absorption of water and chloride. The cytokine also reduced the percentage recovery of the Na⁺-K⁺ ATPase activity in crude homogenates of membranes from surface and crypt colonic cells as revealed by the determination of inorganic phosphate released. In addition IL-1beta decreased the protein expression of the Na⁺-K⁺ pump and increased that of the NaKCl2 symporter. It is concluded that IL-1beta has a dual effect: it inhibits the Na⁺-K⁺ pump and consequently NaCl absorption, and up-regulates the NaKCl2 transporter and increases Cl⁻ secretion. The ultimate effect of the two processes is a net decrease in Na⁺⁺ and Cl⁻ absorption and an increase in water retention in the colon leading to the observed diarrhea in inflammatory bowel disease.

Full text

INTRODUCTION

IL-1beta is a pro-inflammatory cytokine that is involved in a broad array of physiological responses. Among these could be listed the classical sickness responses that include fever, decreased food and water intake, increased sleep, exaggerated pain, increased synthesis of prostaglandins and acute phase proteins, stimulation of bone resorption and cartilage breakdown, proliferation of various cell types, alteration in the levels of iron and zinc in blood [1-3] and others... IL-1beta was reported to induce also gastrointestinal disturbances caused by a decrease in gastric and intestinal motility and a decrease in gastric emptying [4]. Elevated levels of the cytokine were reported in inflammatory bowel disease [5] and HIV infection [6] and were always accompanied by diarrhea, suggesting a potential role of IL-1beta in the regulation of water movement in the colon.

Diarrhea may result from a decrease in net water absorption from the colon, which could occur as a consequence of a decrease in electrolyte absorption or an increase in electrolyte secretion [7]. These absorptive and secretory processes are regulated by different transporters [8] that are distributed differently in the apical and basolateral membranes. The mammalian colon absorbs sodium and chloride, and secretes potassium, bicarbonate, and chloride [9]. The neutral NaCl mucosal transport is the predominant sodium absorptive mechanism in the rat and involves the two antiporters Na/H and

Cl/HCO₃ which are coupled by intracellular pH. The sodium gradient established by the Na⁺-K⁺ ATPase provides the driving force for the Na/H exchanger. The secretion of potassium and chloride is also geared indirectly by the Na⁺-K⁺ pump since it is dependent on the activity of the NaKCl₂ symporter, which is itself energized by the Na⁺ + gradient established by the pump, and on luminal electrolyte conductance [9]. Reduction in water absorption from the colon and consequently diarrhea can be expected to occur in the absence of luminal sodium, when sodium absorption is inhibited, while water absorption is expected to increase if potassium or chloride secretion is reduced by inhibition of the NaKCl₂ transporter. Since most of the transport processes in the colon are geared by the sodium gradient established by the Na⁺-K⁺ ATPase, any alteration in electrolyte transport may be the result of an alteration in the sodium-potassium pump itself.

We have demonstrated previously that IL-1beta inhibits, in a dose-dependent manner, the *in vivo* absorption of 3-O-methylglucose from the rat jejunum by reducing the activity of Na⁺-K⁺ ATPase [10]. Whether the cytokine exerts a similar inhibitory effect on the sodium-potassium pump in the colon thus leading to changes in electrolyte transport and diarrhea, has not yet been investigated.

The aim of this work was to study the effect of IL-1beta on net fluid and chloride absorption from the rat colon and to delineate its mechanism of action.

MATERIALS AND METHODS

Male Sprague-Dawley rats (*Rattus norvegicus*) weighing 150-200 g were handled all through in accordance with the *Guide for Laboratory Animal Facilities and Care*, US Department of Health, Education and Welfare.

All chemicals were purchased from Sigma (Sigma Chemical Co., St Louis, MP, USA). Interleukin-1beta was purchased from Endogen (Woburn, MA, USA).

Animal treatments

A dose response study was undertaken. Different doses of IL-1beta (200, 400 or 600 ng) were injected i.p into rats weighing between 150-200 g, 4 hours prior to the beginning of the experiment. This lag period was shown previously [10] to be required for the effect of the cytokine to manifest itself. In all other experiments

the rats received a dose of 400 ng IL-1 β . Control rats always received 200 μ l physiological saline instead of the cytokine. When the effect of furosemide was investigated, it was added to the perfusion buffer at a concentration of 0.6 mM in all the perfusion steps. When cycloheximide was studied, it was injected (10 mg) i.p., 10 min before the injection of IL-1 β .

Measurement of luminal water and chloride movements in the rat colon

Rats were anesthetized by i.p injection of pentobarbital (5 mg/100 g body weight) and laid on a heating pad maintained at 37° C. The abdomen was opened through a midline incision and the colon was isolated, making sure that the mesenteries and vasculature were kept intact. An inlet and outlet catheter, each attached to a polyethylene tubing (i.d 2.4 mm; o.d 4 mm), were introduced at each extremity of the colon. The inlet tubing was connected to a perfusion pump (Harvard App, 90A) the rate of which was maintained at 0.7 ml/min. The outlet tubing drained into a beaker and allowed for the collection of the effluent buffer.

There were two perfusion steps in all experiments. During the first step, the colon was perfused for 15 min with Krebs-improved Ringer buffer (KIRB) (123.3 mM NaCl; 6.17 mM KCl; 3.29 mM CaCl₂ · 7H₂O; 0.78 mM MgSO₄ · 7H₂O; 32.14 mM NaHCO₃; 1.54 mM KH₂PO₄; 6.4 mM sodium pyruvate; 6.4 mM sodium glutamate; 7 mM sodium fumarate; 11.1 mM glucose) to clear it from wastes. In the second step, the colon was perfused with the same buffer and at the same rate for 30 min. The effluent buffer was collected and its volume measured. In the sodium-free buffer, NaCl and NaHCO₃ were replaced respectively with choline chloride and KHCO₃, while sodium fumarate, sodium pyruvate and sodium glutamate were replaced with mannitol to maintain the same osmolarity. Furosemide was added at a concentration of 0.6 mM during the two perfusion steps. All buffers used were oxygenated (95% O₂, 5% CO₂) at 37° C and their pH adjusted to 7.4.

At the end of the second perfusion, the colon was excised, cut longitudinally, its width and length measured, and its surface area determined. Water movements during the second 30-min perfusion step were calculated as the difference in volume between the infused and collected buffers divided by the surface area of the perfused colon.

Chloride in the infused and collected buffers was measured by titration according to Mohr's method [11] and net chloride absorption was calculated as the difference between the total number of moles present in the 2 buffers, divided by the area of the colon perfused.

Preparation of crude membranes from colonic surface and crypt cells

Surface and crypt cells were isolated from the colon and characterized as described by Homaidan *et al.* [12]. The isolated cells were homogenized in Tris buffer (200 mM NaCl; 5 mM MgCl₂.6H₂O; 2 mM EGTA; 5 mM KCL; 200 mM Tris-HCl, pH 7.4) in a glass-Teflon homogenizer with 20 strokes at 2 100 rpm (Arthur Thomas Scientific Apparatus, Philadelphia, PA, USA) and then spun for 10 min at 1 000 g and 4° C. A crude membrane fraction was then prepared by centrifuging the supernatant collected, for 10 min at 3 300 g, and used to assay for the Na⁺-K⁺ ATPase activity as described below. All steps in the preparation of the homogenate were conducted at 4° C.

Effect of IL-1beta on the activity of the Na⁺-K⁺ ATPase of colonic surface and crypt cell membranes

Crude membranes were diluted with Tris to a concentration of 2 mg protein/ml and used to assess the activity of the Na⁺-K⁺ ATPase. After a 30-min incubation period with saponin (0.02% final concentration) at room temperature, samples (50 µl) were preincubated at 37° C for 10 min in the presence or absence of ouabain (1.25 mM final concentration). The reaction was then initiated by addition of ATP to a final concentration of 4 mM, and terminated after an one hour incubation at 37° C by addition of trichloroacetic acid (200 µl, 11%). The samples were centrifuged at 3 000 g for 5 min and the amount of inorganic phosphate liberated in the supernatant was measured colorimetrically according to the method of Taussky and Shorr [13]. The activity of the enzyme was determined by measuring the ouabain-inhibitable inorganic phosphate released.

The percentage inhibition of the enzyme activity was calculated as follows:

$$1 - [Pi(IL1beta) - Pi(IL1beta + ouabain)] / [Pi(control) - Pi(control + ouabai)] \times 100$$

Western blot analysis

Membrane proteins were resolved on 8% polyacrylamide gels using a Mini-Protean 3 system (Bio-Rad, CA, USA). The samples are warmed to 37° C for 30-45 minutes before loading and transferred to a PVDF membrane (Bio-Rad CA, USA) using a Biorad Mini-Transblot module. The running buffer and the transfer buffer had respectively the following composition: (Tris base: 3 g/l, glycine: 14.4 g/l, SDS 1 g/l) and (Tris base 4.153 g/l; glycine 2.93 g/l; SDS 0.0375 g/l; Methanol: 200 ml). The PVDF membrane was then washed twice with water and blocked in freshly prepared PBS containing 5% skimmed milk and 0.1% Tween for 60 minutes. It was then incubated overnight at 4° C with a rabbit polyclonal anti-Na⁺/K⁺ATPase alpha-1 IgG cat # 06-520 (Upstate Biotechnology, Lake Placid, NY, USA 12946), or with a rat sodium potassium chloride cotransporter antibody (anti-rat NKCC1 cat # NKCC 11-A, Alpha Diagnostic International, TX, USA), at respective concentrations of 0.5 mug/ml and 2 mug/ml. The membrane was then washed twice with PBS-0.1% Tween and incubated with a goat anti-rabbit HRP conjugated IgG (Upstate Biotechnology: cat # 12-348) used at a 1:5,000 dilution in blocking buffer for 1.5 hour at room temperature. This was followed by three washes with PBS buffer containing 1 M Tris and 10% Triton X. Detection of the signal was by enhanced chemiluminescence using luminol reagent (Santa Cruz Biotechnology Inc. CA, USA).

Statistical analysis

Results are reported as means ± SEM. Statistical significance was tested by a one-way analysis of variance followed by a Tukey-Kramer multiple comparisons test.

RESULTS

Effect of different doses of IL-1beta on net fluid absorption from the colon

IL-1beta inhibited, dose-dependently, net fluid absorption from the rat colon (*Table 1*). This inhibitory effect was apparent at all doses tested.

Effect of IL-1beta (400 ng) and inhibitors of some electrolyte transporters on net fluid and chloride absorption from the colon

IL-1beta significantly inhibited net water and net chloride absorption from the colon (*Table 2*). This effect was still apparent in the presence of furosemide or in

the absence of luminal sodium, but disappeared upon simultaneous addition of furosemide and sodium omission (*Table 2*).

Effect of IL-1beta on the activity of Na^+ - K^+ ATPase

The cytokine significantly inhibited, and at all doses tested, the activity of the Na^+ - K^+ pump in both surface and crypt cells (*Table 3*). The inhibitory effect was dose-dependent. Surface cells showed a higher sensitivity to the cytokine and were already inhibited maximally at a dose of 400 ng, while in crypt cells, a significant inhibition was observed with IL-1beta doses from 400 to 600 ng.

Western blot analysis

A - Na^+ - K^+ ATPase expression

In surface cells, IL-1beta significantly reduced the protein expression of the alpha1 subunit of the Na^+ - K^+ ATPase at all doses tested (Figure 1). The observed down-regulation was greater at doses of 400 and 600 ng than at 200 ng, and correlated very well with the observed decrease in the pump activity.

In crypt cells, the alpha1 subunit of the pump was also down-regulated in a dose-dependent manner. The protein expression of the pump at 200 and 400 ng was lower than the control, and dropped further at 600 ng. These results are in line with the observed reduction in the activity of the pump as assessed by Pi measurements.

B - NaKCl_2 expression

IL-1beta caused a dose-dependent overexpression of the NaKCl_2 cotransporter in both surface and crypt colonic cells (Figure 2).

Effect of cycloheximide on water and chloride absorption

The protein synthesis inhibitor, cycloheximide did not affect net fluid absorption in the presence or absence of IL-1beta (*Table 4*). In IL-1beta-treated rats however, a smaller reduction in chloride absorption was observed in presence of cycloheximide.

DISCUSSION

IL-1 β significantly reduced net fluid absorption from the colon thus demonstrating an involvement of the cytokine in the diarrhea observed in inflammatory bowel disease. This effect of IL-1 β may be due to a decrease in water absorption or an increase in water secretion, or both.

Net fluid transport is usually secondary to net electrolyte movements and in the rat it is directly dependent on the rate of Na⁺ transport [14]. Net Na⁺ absorption in the rat colon is electroneutral [15] and is mediated through a coupling of the Na-H and Cl-HCO₃ exchangers.

In this work, inhibiting Na⁺ absorption by sodium omission from the perfusion buffer, significantly reduced net fluid absorption and a greater reduction was observed when animals were treated with IL-1 β . Since the sodium absorption process is already inhibited, the effect of the cytokine may be mediated through another mechanism, possibly involving an increase in fluid secretion.

The secretory processes in the rat colon are dependent on the NaKCl₂ transporter. Inhibition of this carrier with furosemide can be expected to reduce electrolyte and water secretion, and increase net water absorption. Furosemide, as expected, significantly increased water absorption (*Table 2*), revealing the underlying role of the secretory processes in regulating water movements in the basal state. In the presence of furosemide, IL-1 β still reduced net water absorption as compared to furosemide alone, suggesting that the cytokine does not only target secretory processes but may be simultaneously inhibiting absorptive processes. When both electrolyte absorption and secretion were inhibited simultaneously by Na⁺ omission and inhibition of the NaKCl₂ transporter, no significant effect of the cytokine was observed.

IL-1 β had a similar inhibitory profile for net chloride absorption in the absence and presence of furosemide and/or sodium.

The data suggest that IL-1 β has a dual effect: it enhances the secretion of electrolytes and inhibits their absorption. Such effects of IL-1 β have also been reported by other workers. Chiossone *et al.* [16] demonstrated a decrease in Na⁺ and Cl⁻ absorption in the rabbit ileum with IL-1 β , while others [17, 18]

showed an IL-1beta -induced increase in Cl^- secretion in the rabbit distal colon and in patients with ulcerative colitis.

The Na-H exchanger plays a pivotal role in the absorption of NaCl from the rat colon. Luminal sodium entry through this transporter is geared by the sodium gradient established by the $\text{Na}^+ - \text{K}^+$ pump in the basolateral membrane. Any change in this gradient can be expected to alter NaCl absorption and consequently net fluid transport.

This work has shown that IL-1beta decreases the percent recovery of the $\text{Na}^+ - \text{K}^+$ ATPase activity at all doses tested and by so doing dissipates the gradient needed for the electroneutral NaCl transport. The observed inhibition of the pump could be ascribed to a decrease in the number of ATPase molecules present, with no change in their activity or to an inhibition of the ones present with no change in their number.

The $\text{Na}^+ - \text{K}^+$ ATPase is composed of two subunits: alpha and beta. The alpha subunit is the catalytic subunit and contains the binding sites for the cations, ATP and ouabain. [19, 20]. The beta subunit is needed for the proper functioning of the enzyme and modulates its Na^+ and K^+ affinity [21]. Several isoforms of the two subunits have been identified, the alpha1beta1 being the prominent combination present in the colon [22]. To determine the mechanism behind the observed inhibition of the pump, western blot analysis of the alpha1 subunit was conducted. IL-1beta was found to decrease the protein expression of the catalytic alpha1 subunit in both crypt and surface epithelial cells of the rat colon.

This reduction in the number of ATPase molecules is expected to reduce sodium extrusion from the cell and lower the sodium gradient that energizes the Na-H exchanger and luminal sodium entry. Although it is commonly believed that crypt cells are involved in secretion and surface cells in absorption, Singh *et al.* [23] showed that absorption is not restricted to surface cells only, but is also a property of the colonic crypt cells which perform both absorptive and secretory functions.

By down-regulating the $\text{Na}^+ - \text{K}^+$ pump, IL-1beta reduces the sodium gradient needed for the electroneutral NaCl absorption and consequently fluid absorption.

The rat colon secretes also Cl^- which is moved intracellularly by the NaKCl_2 symporter situated on the basolateral side. The inward Cl^- movement is driven by the sodium gradient generated by the $\text{Na}^+ - \text{K}^+$ ATPase and by the Cl^- chemical gradient. Chloride ions accumulate in the cell above their electrochemical equilibrium and leave the cell at the apical side through chloride channels.

This work has demonstrated a reduction in net chloride absorption with IL-1beta, which could be a consequence of the decreased NaCl absorption. When absorptive processes were inhibited by sodium omission from the perfusion buffer, the cytokine was still able to reduce net Cl^- absorption, probably by stimulating Cl^- secretion through an activation of the NaKCl_2 cotransporter. The cytokine had no effect on colonic chloride transport when both absorptive and secretory processes were inhibited by sodium omission and furosemide addition respectively.

CONCLUSION

It could be concluded that IL-1beta inhibits NaCl absorption by inhibiting the $\text{Na}^+ - \text{K}^+$ -ATPase and stimulates Cl^- secretion by stimulating the NaKCl_2 symporter. The activation of the symporter may be secondary to the inhibition of the absorptive process. The decrease in luminal NaCl absorption reduces the intracellular Cl^- concentration, and increases the Cl^- gradient across the basolateral membrane. Payne *et al.* [24] reported that with low intracellular Cl^- , the Cl^- chemical gradient becomes the major contributor to the driving force for the inflow of Cl^- by the NaKCl_2 transporter since 2 Cl^- ions are transported for every K^+ and Na^+ ion.

In addition, western blot analysis demonstrated an up-regulation of the transporter in surface and crypt cells, which is in agreement with the observed lower inhibition in Cl^- absorption in animals treated with cycloheximide.

It can be concluded that IL-1beta down-regulates, in a dose-dependent manner, the $\text{Na}^+ - \text{K}^+$ pump and concomitantly reduces its total activity leading to a dissipation of the Na^+ gradient that gears the transport processes and indirectly, net water movements. As a consequence, net Na, and Cl^- absorption is reduced. IL-1beta also up-regulates the NaKCl_2 transporter and stimulates Cl^- secretion. The ultimate net effect of the cytokine would be a lower net water

absorption from the colon that would confirm the suggested involvement of IL-1beta in the diarrhea observed in inflammatory bowel disease.

Acknowledgements. This work was supported by a grant from the University Research Board.

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Figures

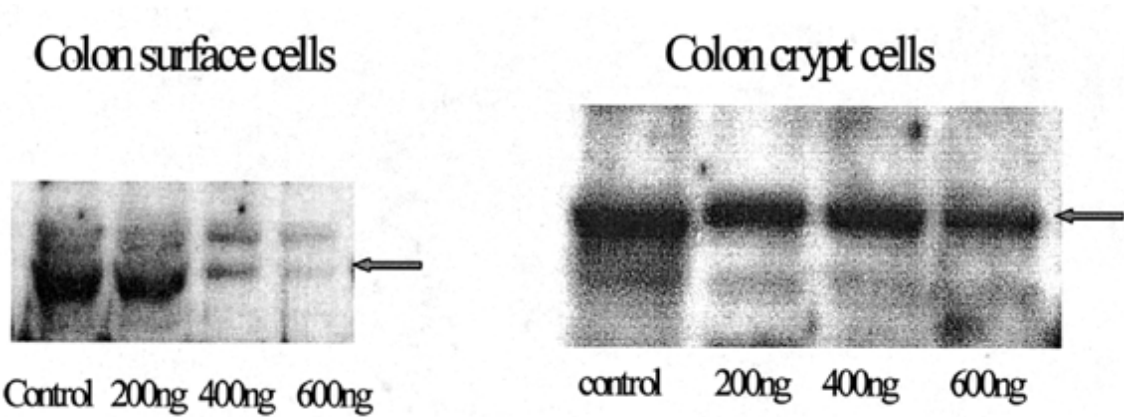


Figure 1	
	Effect of different doses of IL-1beta on Na ⁺ -K ⁺ expression in rat surface and crypt colonic cells.

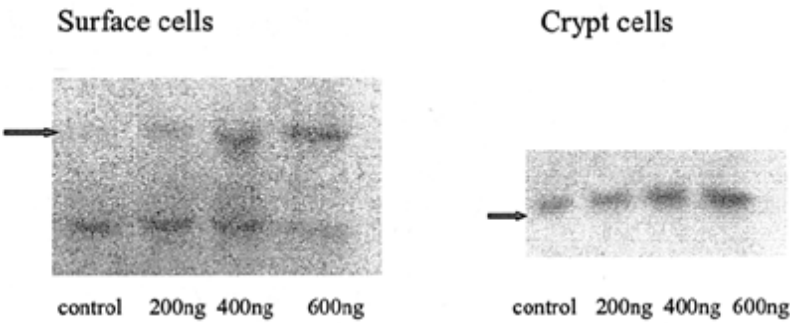


Figure 2

Effect of different doses of IL-1beta on NaKCl₂ expression in surface and crypt cells of the rat colon.

Table 1
Effect of different doses of IL-1β on water absorption from the rat colon

Treatment	N	μl H ₂ O/cm ² *
Control	6	250 ± 20 (A)
IL-1beta (200 ng)	6	170 ± 15 (B)
IL-1beta (400 ng)	6	110 ± 13 (C)
IL-1beta (600 ng)	6	65 ± 7 (D)

* Water absorption is calculated as the net volume of water absorbed per cm² during the 30 min perfusion period.
N is the number of animals in each treatment.
Significant differences:
p < 0.01 (A, B).
p < 0.001 (A, C); (A, D); (B, C).
p < 0.05 (B, D).

Table 2
Effect of different treatments on chloride
and water absorption from the rat colon

Treatment	N	$\mu\text{l H}_2\text{O}/\text{cm}^2$ *	nmol Cl/cm ² *
Control	6	250 ± 20 (A)	41 ± 3 (I)
IL-1beta	6	110 ± 13 (B)	10 ± 0.8 (J)
Furosemide	6	410 ± 38 (C)	63 ± 5 (K)
IL-1beta + furosemide	6	270 ± 30 (D)	38 ± 4 (L)
Na ⁺ -free	6	116 ± 12 (E)	21 ± 2 (M)
Na ⁺ -free + IL-1beta	6	57 ± 6 (F)	34 ± 3 (N)
Na ⁺ -free + furosemide	6	260 ± 30 (G)	40 ± 4 (O)
Na ⁺ -free + furosemide + IL-1beta	6		280 ± 30 (H)

* Chloride and water absorption are measured over the 30 min perfusion period.

N = number of animals in each treatment

Significant differences:

p < 0.05: (L, M).

p < 0.01: (A, B), (A, C), (A, E), (B, G), (C, D), (C, G), (D, E), (E, G), (I, M), (M, O).

p < 0.001: (A, F), (B, C), (B, D), (B, H), (C, E), (C, F), (D, F), (E, H), (F, G), (F, H), (I, J), (I, K), (J, K), (J, L), (J, N), (J, O), (J, P), (K, L), (K, M), (K, N), (K, O), (K, P).

Table 3
Effect of IL-1β on the percentage recovery
of Na⁺-K⁺ ATPase in surface and crypt cells of the rat colon

% recovery of the Na ⁺ -K ⁺ ATPase in the rat colonocytes*		
Treatment	Colon crypt cells	Colon villus cells
200 ng IL-1beta	31 ± 4.1 (A)	51 ± 5.2 (D)
400 ng IL-1beta	38 ± 3.7 (B)	15 ± 2.0 (E)
600 ng IL-1beta	6 ± 0.9 (C)	22 ± 3.3 (F)

* Values are means ± SEM of triplicates.

p < 0.01: (A, C), (B, C), (D, E), (D, F).

Table 4
Effect of cycloheximide on water and chloride absorption from the rat colon in the presence and absence of IL-1β

Treatment	N	μl H ₂ O/cm ² *	mmoles Cl ⁻ /cm ² *
Control	6	250 ± 20 (A)	41 ± 3 (E)
Cycloheximide	6	220 ± 18 (B)	37 ± 3.2 (F)
IL-1beta	6	110 ± 10 (C)	10 ± 0.8 (G)
IL-1beta + cycloheximide	6	130 ± 12 (D)	21 ± 1.3 (H)

*Chloride and water absorption are measured over the 30 min perfusion period.
p < 0.001 (A, C), (A, D), (B, C), (E, G), (E, H), (F, G), (F, H), (G, H).
p < 0.01 (B, D).
p < 0.05 (E, F).

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