

Effects of Orally Administered Epidermal Growth Factor on Enteropathogenic *Escherichia coli* Infection in Rabbits

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The increased intestinal absorption induced by epidermal growth factor (EGF) is associated with diffuse lengthening of brush border microvilli. The aim of this study was to examine the *in vivo* effects of oral administration of EGF during infection with enteropathogenic *Escherichia coli*. New Zealand White rabbits (4 weeks old) received orogastric EGF daily starting 3 days prior to infection with enteropathogenic *E. coli* RDEC-1 and were compared with sham-treated infected animals and uninfected controls. Weight gain, food intake, fecal *E. coli*, and stool consistency were assessed daily. On day 10, segments of jejunum, ileum, proximal, and distal colon were assessed for gram-negative bacterial colonization, disaccharidase activities, and epithelial ultrastructure. Effects of EGF on *E. coli* RDEC-1 proliferation were studied *in vitro*. *E. coli* RDEC-1 caused diarrhea and reduced weight gain. Seven days postinfection, the small and large intestines were colonized with numerous bacteria, brush border microvilli were disrupted, and maltase and sucrase activities were significantly reduced in the jejunum. Daily treatment with EGF prevented the occurrence of diarrhea and reduction of weight gain. These effects were associated with significant inhibition of *E. coli* colonization in the small and large intestine, improved jejunal maltase and sucrase activities and reduced microvillous injury. EGF did not affect the proliferation of *E. coli* *in vitro*. The findings suggest that EGF protects the gastrointestinal tract against colonization by enteropathogenic *E. coli*.

Epidermal growth factor (EGF), a 53-amino-acid polypeptide, is synthesized in the salivary glands and kidneys, and, to a lesser extent, in the lactating mammary glands, small intestine, liver, and pancreas (2, 34). EGF has been implicated in the regulation of a number of physiological and pathophysiological processes, including cellular proliferation (44), wound repair (3), neoplasia (1), and gastrointestinal maturation (4, 30). Studies *in vivo* and *in vitro* have shown that in the intestine, EGF stimulates DNA synthesis and ornithine decarboxylase (12), accelerates brush border disaccharidase maturation (13, 15), and up-regulates absorption of amino acids and carbohydrates (4, 19, 37). EGF exerts its bioactivities in the small as well as the large intestine (22). In the small intestine, the EGF-induced enhancement of nutrient transport is associated with an overall increase in brush border surface area (17, 30). A closely related peptide which also binds to the EGF receptor, transforming growth factor alpha, does not produce this effect, implying that the biological effects of EGF are ligand specific (18).

The interaction of pathogens with the enteric brush border membrane of the host plays a seminal role in the pathogenesis of diarrhea in a number of viral and bacterial infections. Although the plasmid-encoded AF/R1 pilus adhesion of RDEC-1 binds to a transmembrane receptor that is distinct from the EGF receptor (36), *Salmonella typhimurium*, reovirus, and vaccinia virus appear to initiate cellular invasion, at least in part, by binding to the EGF receptor (11, 14, 38). EGF has been shown to promote mucosal healing in experimental colitis and gastroduodenal ulcers in rats, and a recent report suggested that oral EGF administration may accelerate intestinal recovery in piglets infected with rotavirus (24, 35, 46). A number of

studies suggest that luminal EGF is a potent stimulant for mucosal repair in the damaged gastrointestinal tract (32). However, the effects of EGF on epithelial colonization by an enteric pathogen have not been assessed.

Enteropathogenic *E. coli* infections are thought to be the leading cause of death from bacterium-mediated diarrheal disease worldwide, and symptoms are most severe in young children from developing countries (25). Enteropathogenic *E. coli* is an example of a pathogen that induces diarrhea by mechanisms distinct from enterotoxin production or tissue invasion. The infection produces attaching-effacing lesions characterized by loss of microvillous structures at sites of bacterial attachment (25). This injury is associated with brush border enzyme deficiencies, sodium malabsorption, and chloride secretion which, combined, are responsible for the malabsorptive-secretory diarrhea seen in enteropathogenic *E. coli* infections (28, 40, 41). Malabsorptive diarrhea implicating diffuse injury to the epithelial brush border also results from infections with other enteropathogens, including *Giardia* sp. and *Yersinia enterocolitica*, as well as in intestinal anaphylaxis and Crohn's disease (5, 6, 8, 10).

Clearly, EGF has numerous physiological benefits on the intestinal mucosa and profound effects on epithelial turnover and microvillous ultrastructure. The aim of this study was to examine the effects of oral EGF administration on intestinal colonization with enteropathogenic *E. coli*.

MATERIALS AND METHODS

Bacterial strain. Noninvasive, attaching-effacing *E. coli* O15 (RDEC-1) obtained from the American Type Culture Collection was used in all experiments. This strain causes diarrhea in rabbits without producing heat-labile or heat-stable enterotoxins, similarly to enteropathogenic *E. coli* in humans (25). Stock cultures of RDEC-1 bacteria were stored at -70°C in tryptic soy broth (TSB; Difco Laboratories, Detroit, Mich.) coated onto Microbank porous beads (Pro-Labs Diagnostics, Richmond Hill, Ontario, Canada). At the time of study, one bead was deposited into TSB, *E. coli* was allowed to grow overnight, and late-log-phase bacteria were suspended in 10% sodium bicarbonate in phosphate-buff-

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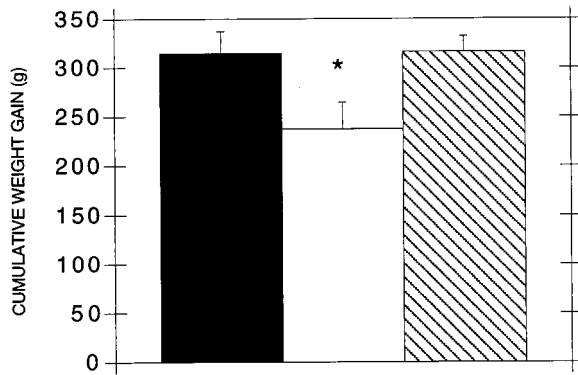


FIG. 1. Cumulative weight gain in control (■), infected untreated (□), or infected EGF-treated (▨) rabbits from days 1 to 7 after infection with *E. coli* RDEC-1 or sham inoculation. *, $P < 0.05$ versus control and EGF-treated rabbits. Values are means \pm SEM.

ered saline (PBS) at a concentration of 2×10^6 CFU/ml as determined by spectrophotometry (405 nm).

Animal model. The model used in this study has been described by Cantey and Blake (7). Human recombinant EGF (Austral Biologicals, San Ramon, Calif.) was used in all experiments. A number of reports have established that human EGF is cross-reactive in several other species, including rabbits (4, 13, 17, 19, 22, 24, 29, 30, 35). Weanling 4-week-old New Zealand White rabbits (mean weight, 709 ± 28 g) were assigned to three experimental groups: (i) infected treated (given 60 μ g of orogastric EGF in 5 ml of sterile PBS daily for 10 days and inoculated with 10^7 *E. coli* RDEC in 5 ml of 10% NaHCO_3 on day 3 [$n = 9$]); (ii) infected untreated (given sterile PBS daily and inoculated with 10^7 *E. coli* RDEC on day 3 [$n = 10$]); and (iii) controls (given sterile PBS daily and 10% NaHCO_3 on day 3 [$n = 9$]). All inocula were delivered orogastrically with a 5-in. blunt feeding needle. Rabbits were housed individually at 24°C, 40% humidity, and 12-h:12-h photoperiods, and they received water and pellets (Unifeed, Calgary, Alberta, Canada) ad libitum.

Weight gain, food intake (calculated from the weight of chow remaining after each day of feeding), and signs of diarrhea were assessed daily. Diarrhea was recorded as present when either perineal soiling could be seen or soft and unformed stool was recovered from rectal swabs. All observations were recorded between 9:00 and 11:00 a.m. to minimize diurnal variations. Fecal passage of *E. coli* RDEC-1 was assessed from daily rectal swabs plated onto MacConkey agar (Difco). Fecal shedding was recorded as positive when lactose-fermenting gram-negative bacteria were recovered on MacConkey plates after overnight incubation at 37°C or as negative when no lactose-fermenting bacteria grew on MacConkey plates after overnight incubation. Animals were killed on day 10 (i.e., 7 days after *E. coli* infection or sham inoculation) by an intraperitoneal overdose of sodium pentobarbital (Euthanyl; MTC Pharmaceuticals, Cambridge, Ontario, Canada). Segments (total of 12 cm) of proximal jejunum (2 cm distal to the ligament of Treitz), ileum (12 cm proximal to the ileocecal junction), proximal colon (distal to the appendix), and distal colon (15 cm proximal to the rectum) were removed and prepared for measurement of disaccharidase activity and mucosal wet weights, bacterial counts, and transmission electron microscopy. All experimental procedures were carried out according to the guidelines of the University of Calgary Committee on Animal Care and Use and the Canadian Council of Animal Care.

Bacterial recovery. Bacterial recovery was assessed from quantitative cultures performed on intestinal segments flushed with sterile PBS and homogenized in sterile PBS. Viable lactose-fermenting *E. coli* cells from intestinal homogenates

were counted by serial dilution and culture on MacConkey agar for 18 h at 37°C. Bacterial colonization was expressed as \log_{10} CFU per centimeter of gut. The difference between bacterial numbers in segments from EGF-treated and untreated animals was calculated and expressed as a percentage of the average number of microorganisms found in the samples from the infected untreated group. This number was referred to as *E. coli* clearance.

Mucosal disaccharidases. Mucosa was scraped with a glass slide, weighed, homogenized in 2.5 mM EDTA, and frozen at -70°C until analyzed for enzyme activities. To assess the effects of the various experimental treatments on overall mucosal content per unit of intestinal length, weights of mucosal scrapings (i.e., mucosal wet weights) were expressed in milligrams per centimeter of gut. Maltase and sucrase were measured by the method of Dahlqvist (9). Protein concentration was assessed by a Bradford protein assay (Bio-Rad Laboratories, Hercules, Calif.), and enzyme activities were expressed as units per gram of protein.

Transmission electron microscopy. Immediately after removal, intestinal tissues for transmission electron microscopy were immersed into 5% glutaraldehyde in Sorensen's phosphate buffer, cut into 1-mm cubes, and stored in the fixative overnight at 4°C. Specimens were washed in buffer, postfixed in 1% OSO_4 , dehydrated in ethanol, cleared with propylene oxide, and embedded in Spurr's low-viscosity medium (J.B. EM Services Inc., Dorval, Quebec, Canada). Sections (90 nm) were stained with saturated uranyl acetate in 50% ethanol, followed by 0.4% lead citrate (43). Specimens were examined on a Hitachi 7000 transmission electron microscope at 80 kV. To standardize observations, small intestinal villi were assessed from midvillus areas only, as determined by a low-magnification observation of an entire villus. To avoid observer bias, micrographs were coded before ultrastructural assessment. For each intestinal region, observations were generated from three to five grids obtained from each of five tissue blocks.

Direct effects of EGF on bacteria in vitro. The effects of EGF on bacterial growth were determined in vitro. In a series of three experiments, log-phase *E. coli* RDEC-1 bacteria (10^8 CFU/ml) were added in duplicate to wells on a 96-well plate containing TSB, with either no EGF (control) or various concentrations of EGF (0.1, 1, 10, and 100 μM), in a total volume of 100 μl /well. These concentrations were chosen to reflect the variable physiological range of EGF levels that may be encountered by enteric bacteria in vivo (16). At 1-h intervals (0 to 5 h postinoculation), viable *E. coli* cells in each well were counted by serial dilution and culture on MacConkey agar plates for 18 h at 37°C. Bacterial numbers were expressed as \log_{10} CFU per milliliter.

Statistical analysis. Results were expressed as means \pm standard error of the mean (SEM) and compared by one-way analysis of variance, followed by Student-Newman-Keuls test for multiple-comparison analysis. $P < 0.05$ levels were considered significant.

RESULTS

Clinical observations. Four of ten infected untreated animals showed signs of diarrhea. Rabbits from the infected EGF-treated and control groups remained asymptomatic. Cumulative weight gain from days 1 to 7 postinfection or sham inoculation was significantly lower in infected untreated animals than in controls (Fig. 1). Weight gain in infected EGF-treated animals was significantly higher than in infected untreated animals and not different from that in controls (Fig. 1). Food intake was not significantly different between any group at any day of the study (data not shown). *E. coli* was isolated from rectal swabs of infected untreated and treated animals within 24 to 72 h of infection, and *E. coli* excretion in the stool persisted for the duration of the study. *E. coli* was not detected in controls. Postmortem, three infected untreated animals, but none from the other groups, showed evidence of a fluid-filled bowel.

TABLE 1. Effects of EGF on live bacterial recovery from intestinal mucosal homogenates of rabbits infected for 7 days with *E. coli* RDEC-1

Group (<i>n</i>)	Mean live bacterial recovery (\log_{10} CFU/cm of gut) \pm SEM ^a			
	Jejunum	Ileum	Proximal colon	Distal colon
Infected untreated (10)	4.19 ± 0.26	6.16 ± 0.26	4.92 ± 0.29	5.16 ± 0.19
Infected EGF treated (9)	$3.10 \pm 0.41^*$	$4.88 \pm 0.23^{**}$	$4.01 \pm 0.16^*$	4.50 ± 0.28
% Clearance ^b	92.0	94.7	85.5	78.0

^a Calculated from serial dilutions of homogenates plated onto MacConkey agar. No bacteria were recovered from any of the nine control rabbits. *, $P < 0.05$ untreated compared with EGF treated; **, $P < 0.01$ untreated compared with EGF treated.

^b Calculated from absolute numbers of bacteria recovered per centimeter of gut as (total number of bacteria in untreated sample/total number of bacteria in EGF-treated sample)/total number of bacteria in untreated sample.

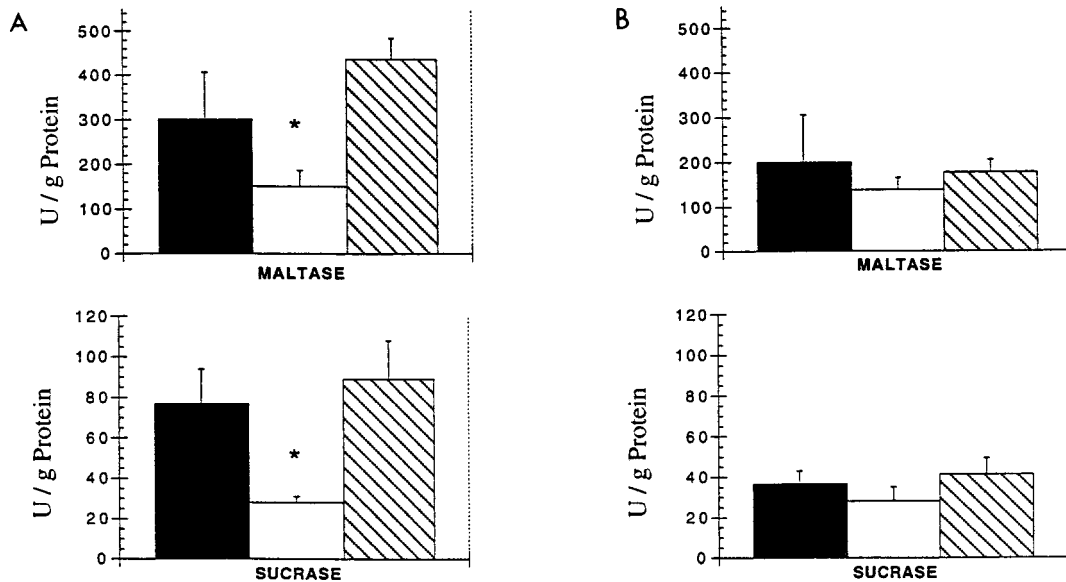


FIG. 2. Maltase and sucrase activities in jejunum (A) and ileum (B) of control (■), infected untreated (□), or infected EGF-treated (▨) rabbits 7 days after infection with *E. coli* RDEC-1 or sham inoculation. *, $P < 0.05$ versus control and EGF-treated rabbits. Values are means \pm SEM.

Bacterial recovery. Viable *E. coli* counts obtained in intestinal specimens from untreated and EGF-treated animals after 7 days of infection are illustrated in Table 1. Bacterial numbers in the jejunum, ileum, and proximal colon of treated rabbits were significantly lower than in untreated animals. Highest bacterial clearance in EGF-treated animals was observed in the jejunum and ileum (92.0 and 94.7%, respectively [Table 1]). Differences in bacterial numbers recovered from distal colon samples failed to reach statistical significance between untreated and treated animals. No *E. coli* organisms were recovered from any intestinal sample in control rabbits.

Disaccharidases and mucosal weights. Mucosal maltase and sucrase activities are illustrated in Fig. 2. Maltase and sucrase activities were significantly reduced in the jejunum of untreated animals infected for 7 days with *E. coli* compared to values obtained from controls. Jejunal enzyme activities in infected animals treated with EGF were significantly higher than in infected untreated animals and were not different from activities in controls. In the ileum, control disaccharidase levels were lower than in the jejunum and enzyme activities were not significantly affected by experimental treatments. Protein contents in mucosal homogenates were not different between any experimental groups at any site (data not shown). Mucosal wet weights of jejunal, ileal, and proximal and distal colonic tissue are shown in Table 2. Wet weights did not differ significantly between any groups in any of the intestinal segments.

Electron microscopy. Jejunal, ileal, and proximal and distal colonic samples from three animals in each group were as-

essed with transmission electron microscopy. Representative results from these observations are illustrated in Fig. 3. After 7 days of *E. coli* infection, numerous gram-negative bacteria were observed in the small and large intestines of infected animals. Bacteria were seen in close association with microvilli, and a number of enterocytes exhibited apical pseudopods devoid of microvilli. Adding to this alteration to the apical membrane, microvilli were shortened along the entire epithelial surface or, in some areas, totally deleted. In samples from EGF-treated rabbits, gram-negative bacteria were found less frequently, and brush border abnormalities were less apparent than in untreated animals. Overall, epithelial ultrastructure in EGF-treated rabbits was similar to that observed in controls (Fig. 3).

Direct effects of EGF on bacteria in vitro. To assess whether the EGF-induced bacterial clearance observed in vivo was due to an antibacterial effect of EGF, growth of *E. coli* RDEC-1 was assessed in vitro in the presence or absence of EGF. In growth medium without EGF, bacterial numbers increased by 4 logs in 5 h (Fig. 4). No difference in bacterial proliferation was observed when 0.1, 1.0, 10, or 100 μ M EGF was added to the medium (Fig. 4).

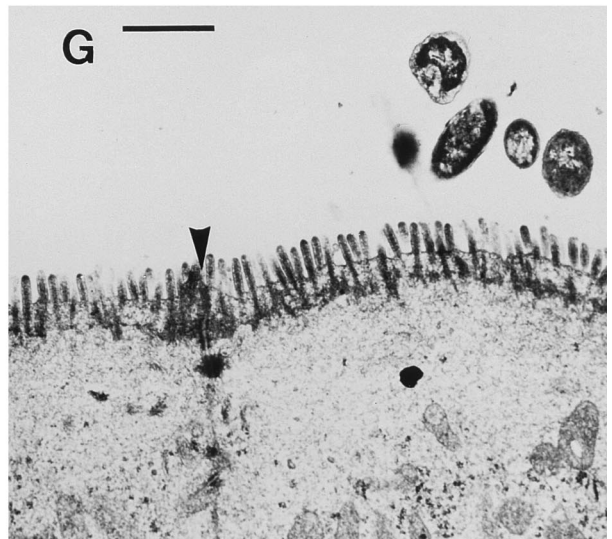
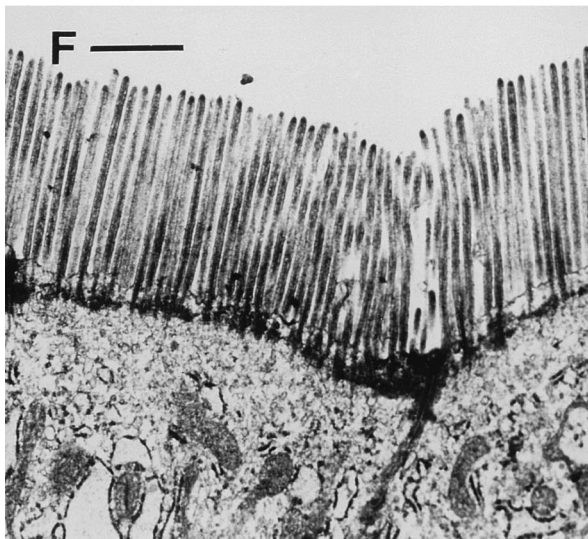
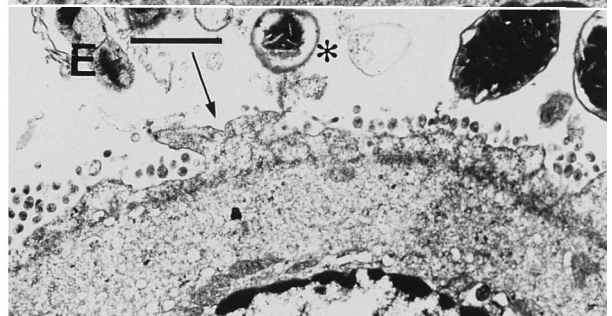
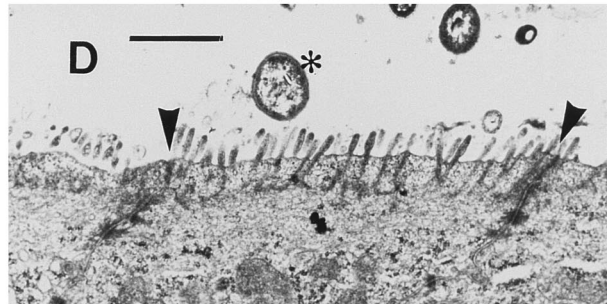
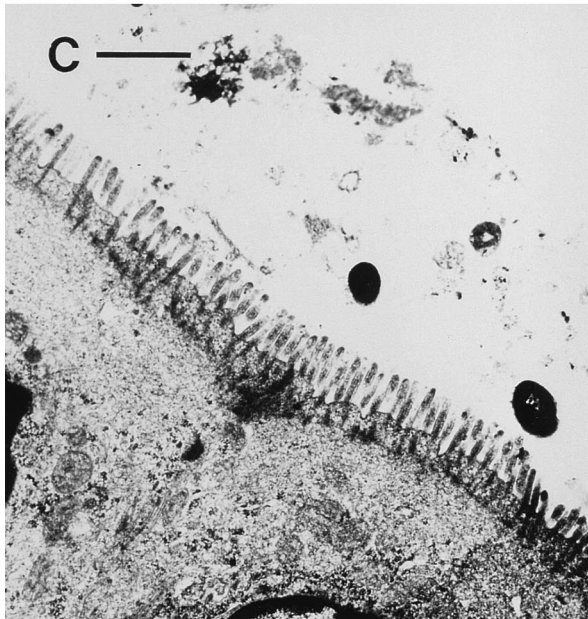
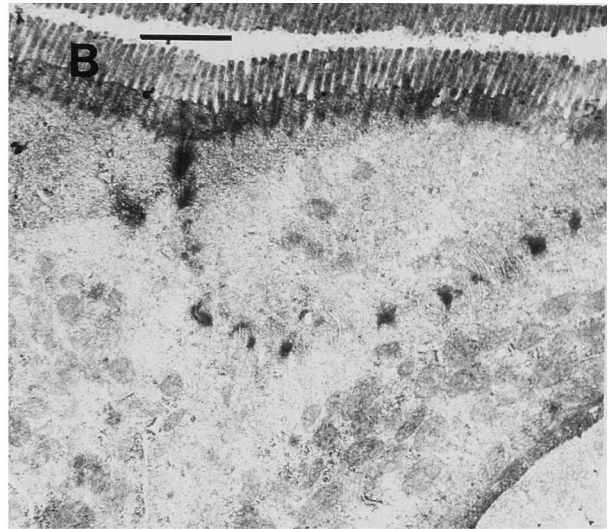
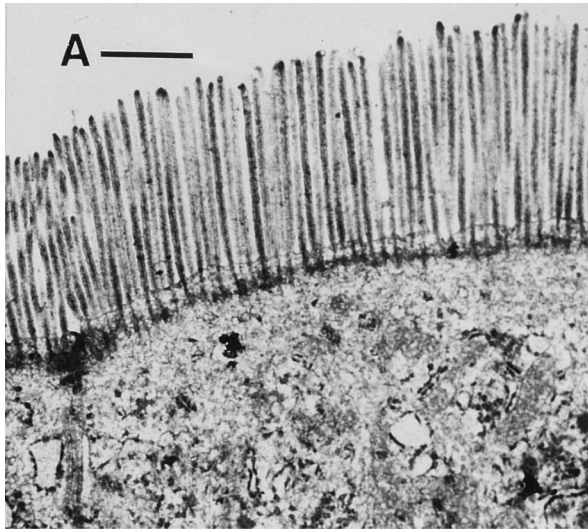
DISCUSSION

This study used an animal model of rabbits infected with enteropathogenic *E. coli* to examine the potential benefits of oral EGF administration in the management of gastrointesti-

TABLE 2. Effects of EGF on mucosal wet weights in the small and large intestines of rabbits infected with *E. coli* RDEC-1

Sample (n)	Mean mucosal wet wt (mg/cm) \pm SE ^a			
	Jejunum	Ileum	Proximal colon	Distal colon
Control (9)	121.6 \pm 18.3	110.2 \pm 8.8	228.2 \pm 18.0	52.1 \pm 3.6
Infected untreated (10)	115.3 \pm 10.6	93.8 \pm 9.8	195.4 \pm 13.5	53.8 \pm 2.9
Infected EGF treated (9)	156.5 \pm 9.6	112.4 \pm 9.3	233.7 \pm 17.5	67.9 \pm 7.8

^a Differences between experimental groups did not reach statistical significance in any segment of the intestine.



nal infections. Compared to control animals, untreated rabbits infected with *E. coli* showed signs of diarrhea and reduced weight gain. After 7 days of infection, high numbers of bacteria colonized the small and large intestine of these animals. Infection was associated with a diffuse disruption to brush border microvilli, and maltase and sucrase activities were significantly impaired in the jejunum. Oral treatment with EGF prevented diarrhea and reduction in weight gain. EGF-treated animals also demonstrated significant bacterial clearance in the small intestine and proximal colon (up to 94.7% bacteria cleared versus untreated). Future studies will assess whether the failure of EGF to significantly reduce bacterial colonization in the distal colon may have resulted at least in part from decreased luminal concentrations of unbound EGF as the peptide transits through the entire length of the gastrointestinal tract. Administration of EGF also prevented the brush border injury and reversed the impairment of jejunal maltase and sucrase activities seen in infected rabbits. Epithelial ultrastructure and disaccharidase activities in EGF-treated infected animals did not differ from control values. EGF alone did not affect multiplication or survival of live bacteria in vitro. The results suggest that EGF administration may be useful in the control of intestinal infection with *E. coli* and that the benefits of EGF are not due to a direct antibacterial effect.

Results from this study confirm the previous clinical and pathological observations on the disease induced in rabbits orally infected with attaching-effacing *E. coli* RDEC-1 (7, 25). In the present study, 4 of 10 animals developed diarrhea. Other authors previously reported 100% rates of diarrhea in animals subjected to similar experimental conditions (45). The fact that these authors assigned a diarrheal score to an animal when soft pellets were found in its cage, while the present experimental design required unformed stool from rectal swabs or perineal soiling, may explain this discrepancy. These experiments also demonstrate that orogastric administration of EGF (100 $\mu\text{g}/\text{kg}$ of body weight daily) prevents bacterial colonization and the subsequent establishment of disease in weanling rabbits. The dosage of EGF used in these experiments is consistent with EGF concentrations delivered to intestinal segments in previous studies (17, 19, 29) and is within the highly variable physiological concentrations of EGF measured in the mature intestine during feeding (16). Following a meal, EGF concentrations in the jejunum can exceed 100 ng/ml (16). In normal weanling mammals, intestinal EGF is significantly lower, and the amount of EGF produced in the salivary glands is known to increase after puberty (23, 27). A recent report demonstrated that oral EGF increases lactase activity in the mid-small intestine of neonatal piglets infected with rotavirus (46). In that study, however, little or no improvement was measured in alkaline phosphatase, leucine aminopeptidase, or maltase activities and, most notably, EGF treatment did not prevent the occurrence of diarrhea in rotavirus-infected piglets (46). Moreover, the effects of EGF administration on viral colonization were not measured. The present report demonstrates for the first time that EGF administration inhibits intestinal colonization by a pathogen and prevents the subsequent development of diarrhea.

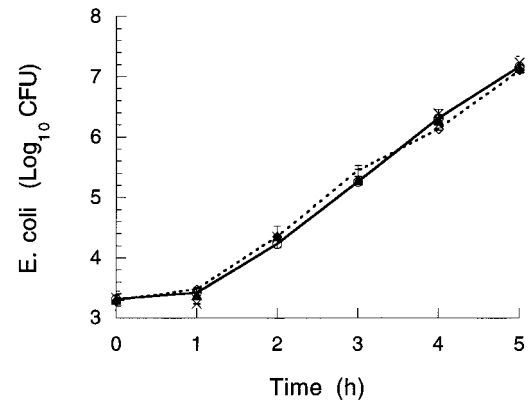


FIG. 4. In vitro proliferation of *E. coli* RDEC-1 in the absence (○) or presence (●) of 10 μM EGF added to the medium. Similar results were obtained when 0.1, 1, or 100 μM EGF was added to the preparations (data not shown). Values are means \pm SEM from three experiments measured in duplicate for each group. No significant difference was observed between values of each group at any time.

The diarrhea seen during infection with enteropathogenic *E. coli* is a result of both chloride secretion and sodium malabsorption (5, 28, 41). EGF has the ability to inhibit chloride secretion and stimulate sodium absorption by altering brush border phosphatidylinositol 3-kinase (21, 42). Furthermore, reduction of brush border microvillus height is a direct cause of malabsorptive diarrhea in a number of intestinal diseases (5, 6, 8, 10, 25). Previous reports have described that *E. coli* RDEC-1 induces a characteristic attaching-effacing lesion on the epithelial brush border (7, 25). In the present study, jejunal colonization with *E. coli* RDEC-1 was associated with generalized disruption of the microvillous brush border, as characterized with formation of apical microvilli-free pseudopods on enterocytes and focal deletion of individual microvilli. The present report adds to the spectrum of *E. coli* RDEC-1-mediated injury a diffuse shortening of brush border microvilli. In the jejunum, these alterations to brush border microvilli were associated with significant impairment of disaccharidase activities. The findings suggest that oral administration of EGF reduces bacterial colonization of the intestinal epithelium, which in turn prevents the brush border lesions associated with enteropathogenic *E. coli* infections in rabbits.

Reports have indicated that in some species, including humans, EGF receptors on enterocytes are located on the basolateral membrane only (33), while they may be found on the apical membrane in others (20). Regardless, the EGF receptor is known to be involved in the initial attachment of some viral and bacterial organisms onto their target cells. Binding to the EGF receptor and activation of its intrinsic tyrosine kinase are required for cellular entry by reovirus (38). Further, occupancy of the EGF receptor on fibroblasts by synthetic peptides of the EGF family inhibits vaccinia virus infection in a dose-dependent fashion (11). Other studies have shown that invasion of epithelial cells by *S. typhimurium* involves binding to the EGF

FIG. 3. Representative transmission electron micrographs (at the same magnification) from jejunum (A, C, and F) and proximal colon (B, D, E, and G) of control (A and B), infected untreated (C to E), or EGF-treated (F and G) rabbits 7 days after infection with *E. coli* RDEC-1 or sham inoculation. In tissues from infected untreated animals, ultrastructural observations revealed colonization by gram-negative bacteria (*), localized deletion of individual microvilli, formation of apical pseudopods devoid of microvilli on enterocytes (arrow), and generalized shortening of microvilli along the entire epithelial surface in the jejunum (C). Bacteria did not invade the epithelium and did not compromise the integrity of junctional complexes (arrowheads). In specimens from the EGF-treated group, gram-negative bacteria were seen less frequently, and disruptions to the epithelial brush border were inhibited. In the jejunum of EGF-treated infected rabbits (F), microvillous length was restored to that observed in tissues from controls (A). Bar = 1 μm .

receptor and subsequent phosphorylation of its intrinsic tyrosine kinase (14). In contrast, it has been demonstrated that *E. coli* RDEC-1 binds, via AF-R1 pili, to an enterocytic membrane glycoprotein receptor complex that is distinct from the EGF receptor (36). This observation suggests that the EGF-mediated inhibition of intestinal colonization by *E. coli* seen in the present study implicates mechanisms which are distinct from competitive binding with the EGF receptor.

Cytokines may directly affect microorganisms. In addition to the classical antiviral effects of interferon, it has been shown that tumor necrosis factor alpha may be lethal to *Pneumocystis carinii* and capable of altering virulence properties of gram-negative bacteria (26, 31). As results from this study demonstrated that oral EGF reduces the colonization by pathogenic *E. coli* in the gut, further experiments sought to assess whether EGF had direct antibacterial effects. EGF alone did not affect *E. coli* proliferation in vitro, which implies that this peptide improves bacterial clearance via mechanisms which are independent of a direct bactericidal or bacteriostatic effect.

The potential value of using EGF as a therapeutic tool to treat gastrointestinal injury has been raised previously. EGF may accelerate healing of gastric ulcers and colitis (24, 35); systemic administration of EGF successfully treated children with necrotizing enteritis (39); and there is experimental evidence to support a therapeutic role for EGF in the management of short gut syndrome (29). Together, these observations suggest that EGF may be a potent stimulant for gut repair. The present study provides evidence that oral EGF therapy may also inhibit colonization of the intestinal tract by pathogens and hence be useful in the control of infectious diarrhea.

In summary, the findings demonstrate that oral EGF administration inhibits the production of diarrhea and reduction in weight gain seen in weanling rabbits infected with attaching-effacing *E. coli*. In the intestine, EGF significantly reduces epithelial colonization by this pathogen, decreases brush border injury, and suppresses disaccharidase impairment. The mechanisms whereby EGF induces these effects have yet to be uncovered, but findings reported herein indicate that they may operate independently from competitive binding to the EGF receptor or a direct antibacterial effect of the polypeptide. Adding to the well-described role of EGF as a repair and maturation stimulant in the gut, these observations suggest a role for EGF in protecting the gastrointestinal tract from colonization by bacterial pathogens.

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