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Effect of Glucocorticoid on Piglet Jejunal Mucosa during Acute Viral Enteritis[1]

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ABSTRACT. We measured the effect of pharmacological doses of glucocorticoid on piglet jejunal structure and function during acute viral diarrhea. Weaned piglets, infected experimentally with transmissible gastroenteritis virus, a coronavirus that induces a diarrheal illness similar to human rotavirus infection, received methylprednisolone (30 mg/kg) or saline intramuscularly at 48 and 72 h after infection; noninfected littermate controls were similarly injected with methylprednisolone. Animals were killed at 96 h, at the height of diarrhea, and jejunal epithelium was studied *in vitro*. Transmissible gastroenteritis, as expected, induced structural, enzyme, and Na transport abnormalities. Methylprednisolone did not affect small intestinal structure or function of noninfected control piglets. In transmissible gastroenteritis-infected piglets, jejunal villi were longer and glucose-facilitated Na absorption was greater after methylprednisolone than after saline treatment. Increased glucose stimulation of Na flux *in vitro* in the methylprednisolone-treated infected group was not attributable to enhanced Na^+-K^+-ATPase activity and occurred despite persistence of the virus within mucosal cells, shown by immunofluorescense microscopy. In this piglet model of viral diarrhea, early regeneration of absorptive surface that precedes recovery of disaccharidase function is accelerated by glucocorticoid therapy. (*Pediatr Res* 23: 279–282, 1988)

Abbreviations

Isc, short-circuit current
Na, sodium
MP, methylprednisolone
J^{Na}_{ms}, Na flux from mucosa to serosa
J^{Na}_{sm}, Na flux from serosa to mucosa
J^{Na}_{net}, Net Na flux
ΔJ^{Na}_{net}, increment in net Na flux
Na^+-K^+-ATPase, sodium-potassium-stimulated adenosine triphosphatase
TGE, transmissible gastroenteritis
ANOVA, analysis of variance
G, conductance

TGE is an invasive viral enteritis occurring in young pigs (1). The impact of this coronavirus infection on the small intestine resembles that of human rotavirus (1, 2). Watery diarrhea is attributable to a loss of functioning differentiated enterocytes and dominance of the epithelium by relatively undifferentiated cells (1–4).

Glucocorticoids in pharmacological doses may influence small intestinal epithelial differentiation. In suckling rabbits, glucocorticoid accelerates the appearance in the intestinal brush border of active disaccharidases and stimulates precocious development of glucose-facilitated Na transport (5). Furthermore, under some experimental conditions, pharmacological doses of glucocorticoid augment the activity of rat intestinal mucosal Na^+-K^+-ATPase (5–7); in both rats and humans they enhance *in vivo* absorption of Na, water, and glucose (6; 8).

Therefore, we studied the effect of pharmacological doses of MP on the response of piglet small intestine to experimentally induced infection with TGE virus. These experiments focused on the jejunal epithelium, its structure, enzyme activities, and transport function.

MATERIALS AND METHODS

Thirteen York-Landrance piglets, 17–21 days old, were weaned and fed evaporated cow's milk for 3 days. Eight piglets received a standard intragastic inoculum of Purdue strain of TGE virus (1) and five uninfected littermates were used as controls. Three uninfected piglets received MP (30 mg/kg intramuscularly) on the 17th and 18th day of life (control MP). Of the eight TGE-infected pigs, four received MP (30 mg/kg intramuscularly) 48 and 72 h after TGE inoculation (TGE-MP) and the other four were injected with an identical volume of saline (TGE-saline).

For intestinal studies, piglets were killed by a parenteral injection of 325 mg pentobarbital sodium. Beginning 10 cm distal to the ligament of Treitz, the first 10–12 cm of jejunum were removed quickly, flushed with normal saline, stripped of muscle, and mounted in conventional Ussing chambers (exposing an area of 1.29 cm^2) for studies of ion transport (4). The next 25 cm was removed, flushed with saline, and processed as follows: the first 1-cm segment was quick-frozen for viral immunofluorescence; the next cm was fixed in Bouin's solution, blocked in paraffin, and stained with hematoxylin and eosin; and from the remaining 23 cm, mucosa was scraped with a glass slide, homogenized with a Dounce homogenizer, and frozen at −70° C. This frozen homogenate was assayed for sucrase, lactase (9), Na^+-K^+-ATPase (2), and thymidine kinase (4); results are expressed as specific activities.

For ion flux measurements, mucosal and serosal sides of the tissue were bathed at 37° C in 10 ml oxygenated Krebs-Ringer bicarbonate buffer (pH 7.4) containing (mM): Na 143, potassium 10, magnesium 1.11, calcium 1.25, chloride 128, HCO_3 25, H_2PO_4 2, and acetate 3. Acetate was provided for tissue energy metabolism. In each experiment, jejunal tissue was mounted in the chambers within 30 min of the piglet's death and Isc was adjusted at 10-min intervals (10). Transmucosal potential differ-

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ences and conductances were stable indicating tissue viability during each of these 2-h studies. We added ^{22}Na to mucosal or serosal chambers initially and, after a 15-min equilibration period, withdrew 1-ml samples from each chamber at 10-min intervals. We calculated undirectional Na fluxes from the rate of appearance of label in the opposite chamber. After 55 min, we added 5 ml of Krebs buffer containing D-glucose (30 mM final concentration) to the mucosal and serosal chambers, and again measured unidirectional Na fluxes, sampling from the chambers at 10-min intervals for 1 h. We calculated J_{ms}^{Na} and J_{sm}^{Na} using jejunal segments paired so that G did not differ by more than 25%. Net Na flux was calculated by the formula $J_{net}^{Na} = J_{ms}^{Na} - J_{sm}^{Na}$.

Preliminary studies of TGE viral antigen in the mucosa used direct immunofluorescence with fluorescein-conjugated porcine anti-TGE globulin, as previously described (3). Jejunal sections were interpreted, without prior identification, by an observer who routinely performs TGE immunofluorescence. Results were reported as positive (diffuse fluorescence of enterocytes), weakly positive (weak fluorescence of occasional enterocytes), or negative (3). For light microscopic studies, all specimens were examined by the same observer without prior identification, using a calibrated micrometer eye piece to measure 10–15 representative crypt villus units.

^{22}Na was obtained from Amersham (Montreal, Canada), D-glucose from BDH Chemicals (Toronto, Ontario, Canada). The remaining reagents were obtained from Sigma Chemical (St. Louis, MO).

Mucosal structure and enzymes were compared in the four groups of piglets using one-way ANOVA. For data involving comparisons of means between several groups, we used Scheffe's multiple comparisons method (11). For transport studies, Na fluxes under basal conditions were compared with those after adding D-glucose using the *t* test for paired variates. Based on the hypothesis that MP would increase transport (5–8), we compared jejunal Na transport in MP-treated pigs (uninfected, TGE-infected) with Na transport in their corresponding controls using Student's one-tailed *t* test.

Table 1. *Piglet jejunum—light microscopic measurements (mean ± SEM)*

	Control ($n = 2$)	Uninfected-MP ($n = 3$)	TGE-saline ($n = 4$)	TGE-MP ($n = 4$)
Villus ht (μm)	294 ± 8	313 ± 32	86 ± 16*	190 ± 12*†
Crypt depth (μm)	122 ± 2	124 ± 7	231 ± 33	226 ± 29

* $p < 0.05$ compared with controls.

† $p < 0.05$ compared with TGE infected, saline injected.

RESULTS

Clinical findings. No changes in behavior or stooling pattern were noted in uninfected piglets treated with MP. Infected piglets all developed anorexia and appeared ill. Each of the four infected pigs given saline developed diarrhea and demonstrated a fluid-filled small bowel at 96 h. Of the four infected animals injected with MP, three developed diarrhea but only one showed a fluid-filled intestine at 96 h. The four MP-treated infected piglets weighed approximately the same (2390 ± 150 g) as their saline-injected counterparts (2530 ± 160 g). Also, the weights of the proximal and distal small bowel after flushing with saline did not differ in the two groups.

Microscopic studies (Table 1). MP treatment did not alter jejunal structure of uninfected piglets compared with controls. Ninety-six h after TGE infection jejunal villi were blunted ($p < 0.05$) regardless of whether animals had received saline or MP. However, in comparing the two TGE-infected groups, we observed taller villi ($p < 0.05$) and, in most preparations, less inflammation of the lamina propria in MP-treated animals than in saline-treated controls.

In 96-h TGE jejunum, TGE immunofluorescence was only weakly positive in two and negative in the other two preparations from saline-treated piglets. In MP-treated TGE-jejunum at 96 h, three preparations were available for immunofluorescence staining, and, in all of these, immunofluorescence was strongly positive. These preliminary observations suggested MP had delayed viral clearance.

Jejunal mucosal enzymes (Table 2). In uninfected pigs, activities of disaccharidases, Na^+-K^+-ATPase, and thymidine kinase were not altered by MP injection. Reductions of sucrase and Na^+-K^+-ATPase activities were observed in the jejuna of both groups of 96-h TGE-injected piglets (saline-injected and MP-injected) ($p < 0.05$, compared with uninjected controls). While mean thymidine kinase activity tended to be higher and lactase tended to be lower in TGE jejunum than in controls, the results were not statistically significant.

MP had no significant effect on sucrase, lactase, Na^+-K^+-ATPase, or thymidine kinase activities in TGE-infected pigs, regardless of whether activities were related to mucosal protein, intestinal wet weight, or length.

Table 2. *Piglet jejunum-enzyme-specific activities in whole mucosal homogenates (mean ± SEM)*

	Control ($n = 2$)	Uninfected-MP ($n = 3$)	TGE-Saline ($n = 4$)	TGE-MP ($n = 4$)
Sucrase ($\mu mol \cdot g^{-1} \cdot min^{-1}$)	45.7 ± 4.8	48.5 ± 12.7	2.5 ± 0.1*	3.1 ± 0.5*
Lactase ($\mu mol \cdot g^{-1} \cdot min^{-1}$)	56.8 ± 10.9	64.3 ± 22.9	4.4 ± 1.8	5.9 ± 0.8
Na^+-K^+-ATPase (pmol $P_i \cdot mg^{-1}$ min^{-1})	92.5 ± 7.5	98.3 ± 9.7	52.1 ± 2.6*	52.7 ± 4.3*
Thymidine kinase ($pmol \cdot mg^{-1} \cdot h^{-1}$)	10.2 ± 3.0	9.4 ± 1.6	97.2 ± 42.7	100.5 ± 46.2

* $p < 0.05$ compared with controls or uninfected MP.

Table 3. *Piglet jejunum: transmucosal unidirectional and net Na fluxes ($\mu Eq \cdot cm^{-2} \cdot h^{-1}$), Isc ($\mu Eq.\ cm^{-2} \cdot h^{-1}$), and G ($mmho \cdot cm^{-2}$); uninfected pigs (saline vs. MP injected) (mean ± SEM)*

	n	Na Jms	Na Jsm	Na Jnet	Na ΔJnet	Isc	G
Basal							
Control	6	11.3 ± 1.0	12.7 ± 0.8	−1.4 ± 0.4		2.8 ± 0.3	26.8 ± 1.5
Uninfected-MP	6	10.5 ± 0.4	12.8 ± 0.5	−2.3 ± 0.9		2.9 ± 1.5	26.6 ± 1.5
D-glucose (30 mM)							
Control	6	14.1 ± 1.1	11.3 ± 0.7	2.8 ± 0.9*	4.2 ± 1.0	7.9 ± 1.0*	29.9 ± 0.7
Uninfected-MP	6	13.3 ± 0.5	11.7 ± 0.6	1.6 ± 1.0*	3.9 ± 0.7	7.8 ± 0.5*	29.3 ± 0.9

* $p < 0.05$ compared with basal period.

Na transport data. Measured *in vitro* in Ussing chambers, transmucosal unidirectional Na fluxes (J^{Na}_{ms}, J^{Na}_{sm}) and G in uninfected MP-treated pigs did not differ from those of controls (Table 3). After D-glucose (30 mM), J^{Na}_{net} and Isc increased in both groups of uninfected piglets ($p < 0.05$), and there was no difference in the magnitude of these responses between MP-treated ($\Delta J^{Na}_{net} = 4.2 \pm 1.0$ $\mu Eq \cdot cm^{-2} \cdot h^{-1}$) and untreated control tissue ($\Delta J^{Na}_{net} = 3.9 \pm 0.7$ $\mu Eq \cdot cm^{-2} \cdot h^{-1}$) (Fig. 1).

Ussing chamber transport data from 96-h TGE-infected piglets are shown in Table 4 and Figure 1, which compare jejunal Na transport response to D-glucose of MP-injected animals with that of saline-injected litter mates. Basal mucosal to serosal Na flux was modestly enhanced in MP-treated animals, but net Na flux was secretory and did not differ from controls. After 30 mM D-glucose, J^{Na}_{net} increased in both saline-injected and MP-treated TGE jejunum ($p < 0.01$); however, only in the glucocorticoid-treated group did net Na flux become absorptive ($J^{Na}_{net} = 0.6 \pm 0.5$ $\mu Eq \cdot cm^{-2} \cdot h^{-1}$; $p < 0.01$ compared with basal J^{Na}_{net}). The net response to D-glucose in MP-treated piglet jejunum ($\Delta J^{Na}_{net} = 1.6 \pm 0.4$ $\mu Eq \cdot cm^{-2} \cdot h^{-1}$) significantly exceeded response of saline-injected TGE-injected jejunum ($\Delta J^{Na}_{net} = 0.5 \pm 0.2$ $\mu Eq \cdot cm^{-2} \cdot h^{-1}$) (Fig. 1). There were small increases in J^{Na}_{sm} and G after D-glucose in both groups, which were significant only in saline-treated piglets; however, the magnitude of these changes (ΔJ^{Na}_{sm}, ΔG) did not differ between the two groups.

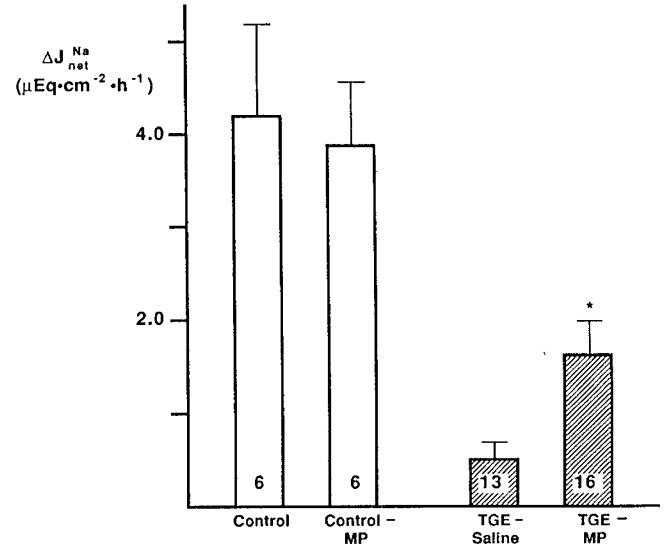

Fig. 1. Increase of net Na flux (ΔJ^{Na}_{net}) in control (*open bars*) and TGE (*shaded bars*) piglet jejunum, measured in Ussing chambers, in response to 30 mM D-glucose. Responses of control and TGE-infected jejuna are compared with normal and TGE-infected pigs injected with MP as described in "Materials and Methods." * $p < 0.05$ compared with saline-injected TGE group.

DISCUSSION

Short-term, high-dose, glucocorticoid treatment of normal piglets did not alter jejunal structure, enzymes, or glucose-facilitated Na transport in the current experiments. Previous studies using similar doses in rats found increased ileal villus height (12), increased disaccharidase activities (12), and enhanced electroneutral NaCl transport (13) in response to corticosteroid. Furthermore, MP (20–30 mg/kg) has been shown to stimulate basal ileal Na and Cl transport (13, 14) and ileal response to combined absorptive stimuli (glucose + alanine + epinephrine) (14) after only 24–48 h of treatment. Because we found MP treatment had no impact on basal jejunal Isc, we conclude that glucocorticoid treatment did not stimulate electrogenic chloride secretion, as reported in rat (15) and rabbit (16) ileum by others. These discrepancies between our data and those reported previously could be attributed to many possible factors, including species specificity, differences in the responses of jejunum and ileum, and the relatively brief period of MP treatment we used.

We gave MP at 48 and 72 h after TGE inoculation because previous studies showed maximal jejunal injury and viral shedding before 40 h after infection (3), when the epithelium is most undifferentiated and presumably most responsive to glucocorticoid (17, 18). As recovery from TGE-induced injury in untreated pigs is complete by 144 h (4) we studied jejunal tissue at 96 h, expecting animals at this stage to show partial villus recovery but little or no virus remaining in the epithelium.

Glucocorticoid treatment clearly did not alter disaccharidase activity in either normal pigs or in those with viral diarrhea. In the normal group, the lack of effect of MP probably reflects a functionally mature mucosal disaccharidase pattern in the weaned animal. However, in the TGE-infected epithelium, low disaccharidase activities persisted after MP treatment, despite a lengthening of villi in MP-treated animals. Studies in suckling rats showed the effects of glucocorticoid require emergence of cells from the crypts, with maximal effects on mucosal sucrase after 120 h (19). Consequently, we expected an earlier response in TGE epithelia, because enterocyte transit time decreases from approximately 55 to 18 h in this disease (3). TGE jejunal cells, therefore, differ from those of the developing gut not only in their rapid proliferation but also in their failure to respond by 48 h to adrenocorticoid by synthesis or activation of brush border digestive enzymes.

In the virus-damaged epithelium, glucocorticoid treatment did enhance functional maturity as reflected by jejunal villus structure and the Na-absorptive response to glucose. Accelerated enterocyte migration, observed after long-term corticosteroid treatment (12), could have contributed to this observation. In previous studies of suckling rabbits treated with cortisone (5) we attributed precocious development of jejunal glucose-facilitated Na transport to increased lumen to cell driving forces resulting from enhanced Na^+-K^+-ATPase activity. However, our current data demonstrate increased glucose-stimulated Na absorption in the weaned piglet in the absence of altered Na^+-K^+-ATPase

Table 4. *Piglet jejunum: transmucosal unidirectional and net Na Fluxes ($\mu Eq \cdot cm^{-2} \cdot h^{-1}$), Isc ($\mu Eq \cdot cm^{-2} \cdot h^{-1}$), and G (mmho·$cm^{-2}$); 96-h TGE-infected pigs (saline vs MP-injected) (mean ± SEM)*

	n	Na Jms	Na Jsm	Na Jnet	Na ΔJnet	Isc	G
Basal							
TGE-saline	13	4.8 ± 0.4	6.4 ± 0.3	−1.6 ± 0.3		1.5 ± 0.1	13.2 ± 0.6
TGE-MP	16	6.0 ± 0.6*	7.1 ± 0.4	−1.0 ± 0.4		1.4 ± 0.1	14.8 ± 1.0
D-glucose (30 mM)							
TGE-saline	13	6.3 ± 0.2†	7.4 ± 0.3†	−1.1 ± 0.2‡	0.5 ± 0.2	3.0 ± 0.3‡	15.8 ± 0.9‡
TGE-MP	16	8.2 ± 0.6*†	7.6 ± 0.4	0.6 ± 0.5*†	1.6 ± 0.4*	3.6 ± 0.3‡	16.4 ± 0.6

* $p < 0.05$ compared with saline-injected group.
† $p < 0.01$ compared with basal Na flux.
‡ $p < 0.05$ compared with basal Na flux.

activity, suggesting that the glucocorticoid effect observed was independent of the activity of the basolateral membrane Na pump. Rapid activation of the Na^+-K^+ pump can occur as a result of a sudden increase in intracellular Na (20). In rabbit descending colon glucocorticoid treatment was recently shown to enhance apical Na permeability (21), which in turn would rapidly activate Na^+-K^+-ATPase. Our data do not preclude MP effects on brush border permeability and/or basolateral pump function but they do indicate that MP does not alter Na^+-K^+-ATPase specific activity in the jejunum and that it has no major effect on basal Na transport in control or TGE jejunum. The augmented jejunal response to D-glucose (ΔJ_{net}^{Na}) we observed in the MP-treated infected piglet is compatible with the hypothesis that glucocorticoid alters brush border glucose-Na cotransport, as observed in intestinal brush border membrane vesicles from rats injected with triamcinolone (22). Alternatively, MP may alter jejunal glucose-Na cotransport simply by increasing absorptive surface area.

Increased glucose-stimulated Na absorption in the treated pigs was not due to enhanced elimination of virus from the epithelium. Our data showing villus blunting and a 10-fold reduction in mucosal disaccharidases in MP-treated infected piglets suggest the drug did not interfere with exfoliation of infected villus cells. However, the finding of homogeneous immunofluorescence of enterocytes at 96 h, in the MP-treated group only, suggests that glucocorticoid treatment may interfere with viral clearance from the mucosa. Determination of the effects of MP on viral clearance was not the aim of the present study and would require sequential quantitation of virus in the mucosa and intestinal fluid. Our finding, however, is compatible with the theory that MP treatment could facilitate persistence of virus beyond the 40-h stage, when it is normally cleared (3).

Although the TGE model in the piglet represents a major human disease, human rotavirus enteritis, our data should not be interpreted to suggest that corticosteroid treatment of babies with severe viral enteritis would be beneficial. In fact, the observation that virus may be retained in the epithelium after MP-treatment suggests such treatment is contraindicated. Our findings do indicate that the relatively undifferentiated epithelium occurring in this acute viral enteritis is responsive to hormonal influences.

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