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Comparative Effects of Glucocorticoids and Prostaglandins on Small Intestine of Infant Rats

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ABSTRACT. Previous studies have suggested similarities between the effects of exogenously administered glucocorticoids and prostaglandins in the developing rat small intestine. In this study the effects of exogenously administered glucocorticoids and prostaglandins were compared. In addition, the effects of prostaglandins in adrenalectomized rats were evaluated. Members of both classes of compounds stimulate small intestinal disaccharidase activities, and increase RNA to DNA ratio and brush border membrane protein synthesis. Hydrocortisone accelerates enterocyte turnover, whereas prostacyclin does not. Enteral administration of 16,16-dimethyl prostaglandinE_2 stimulates disaccharidase activities in intact as well as sham-operated and adrenalectomized animals. The data suggest that certain prostaglandins may play a role in small intestinal metabolism which is similar to that of the glucocorticoids but is independent of the adrenal-intestinal axis. (*Pediatr Res* 20: 109–112, 1986)

Abbreviations

PG, prostaglandin
16,16-DMPGE_2, 16,16-dimethyl PGE_2

Glucocorticoids are known to play a significant role in the development of small intestinal biochemical function. These hormones appear to mediate a series of enzymatic changes in the small intestine of rats during the 3rd wk of postnatal life (1–3). Administration of hydrocortisone or ACTH during the 2nd postnatal wk causes precocious appearance of sucrase activity (4), whereas adrenalectomy at this time markedly slows the usual increase of sucrase activity (5). In adult rats, sucrase activity is independent of glucocorticoids (6).

In a previous study by our group (7), prostaglandins were administered to suckling rats to determine their effects on growth and development. Analysis of small intestinal hydrolase activities demonstrated effects similar to those of the glucocorticoids. Other than this, little information is available regarding the physiological role of prostaglandins in the gastrointestinal tract of the developing fetus and neonate. More recent studies by Koelz *et al.* (8) have demonstrated that an enterally administered prostaglandin analog, 16,16-DMPGE_2, will stimulate disaccharidase activity in the small intestine of suckling but not adult rats.

Since the stimulation of the enzyme activities by the glucocorticoids and prostaglandins are similar in many respects, we decided to investigate further the comparative effects of these two classes of compounds. The purpose of these studies was twofold: 1) to compare the effects of glucocorticoids and prostaglandins in terms of disaccharidase activities, nucleic acid ratio, brush border protein synthesis, and DNA synthesis; and 2) to determine the effects of prostaglandins on small intestinal disaccharidases in intact and adrenalectomized suckling rats. Rats were adrenalectomized in order to determine whether prostaglandins directly affect the intestine or whether these effects occur as a result of stimulation of the adrenal glands.

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MATERIALS AND METHODS

Animals. Infant Sprague-Dawley rats were used in this study. They were caged with their mothers and allowed to suckle *ad libitum* in a temperature and light-controlled environment.

Chemicals and reagents. Cellobiose and lactose were purchased from Calbiochem (La Jolla, CA), sucrose from Mallinckrodt, Inc. (Paris, KY), maltose from Sigma Chemical Company (St. Louis, MO), and Statzyme glucose 500 nm from Worthington (Freehold, New Jersey). Prostacyclin (PGI_2) and 16,16-DMPGE_2 were obtained from the Upjohn Company (Kalamazoo, MI). Reagent grades of DNA (calf thymus type 1) and RNA (*torula* yeast type 6) were obtained from Sigma Chemical Company (St. Louis, MO). Bovine serum albumin was obtained from Eastman (Rochester, NY). Corticosterone ^3H kits were obtained from Radioassay Systems Laboratories, Inc. (Carson, CA; catalogue no 301). ^3H-leucine (40–60 Ci/mmol) was obtained from New England Nuclear. Hydrocortisone sodium succinate (100 mg/2 ml) was obtained from Abbott Laboratories (North Chicago, IL).

Experimental design. One group of studies was done in order to compare the relative effects of subcutaneously administered prostacyclin to hydrocortisone. Another group of studies was done to determine the effects of enterally administered 16,16-DMPGE_2 on intact and adrenalectomized rats. For the studies designed to compare intestinal hydrolase activities, enterocyte turnover time, and brush border membrane disaccharidase synthesis after parenteral administration of prostacyclin or hydrocortisone, three sets of suckling littermates were treated with 0.3 mg/kg PGI_2, 50 mg/kg hydrocortisone or 0.9% saline three times a day by subcutaneous injection in 50 μl volumes. Injections were given subcutaneously in the neck and aimed caudally to eliminate leakage of injectate. In order to insure that PGI_2 was injected in an active form, it was prepared shortly before the injection in 0.0103 M mannitol, 0.25 M NaCl, 0.333 M glycine, and pH 10.5 buffer. The first set, containing two animals per group, received 15 μCi ^3H-thymidine at 18, 36, and 72 h before sacrifice in order to measure cell turnover rate from crypt to villus. A second set of animals was given prostacyclin, hydrocortisone, or saline for studies of DNA synthesis rate. In a third set of animals, ^3H-leucine was administered 18 h before sacrifice to determine protein synthesis. On day 14 of life, these animals were sacrificed by decapitation between 0800 and 1100 h in all studies to eliminate any diurnal effects on intestinal disaccharidase activities. Disaccharidase activity and protein were meas-

ured and DNA and RNA were assayed in the total remaining small intestine (duodenum to distal ileum) of all animals.

For the studies designed to determine the effects of enteral prostaglandins, 16,16-DMPGE$_2$ was administered at a dose of 100 μg/kg twice daily to intact rats on days 9 to 13. These animals were sacrificed on day 14. Triacitin, the 16,16-DMPGE$_2$ vehicle, was administered to control rats. Adrenalectomized or sham-operated littermates were also gavaged with a volume of 50 μl of 16,16-DMPGE$_2$ (100 μg/kg) or Triacitin. For the studies comparing adrenalectomized to sham-operated rats, surgery was performed on day 10 of life. These animals were sacrificed on day 15. Adrenalectomy was done on day 10 by a posterior approach under methoxyfluorane anesthesia. Sham-operated animals had their kidney and adrenals manipulated but without removal of the adrenal glands. Trunk blood was collected at the time of sacrifice for corticosterone radioimmunoassay in order to validate completeness of adrenalectomy. Adrenalectomy was considered complete only if no adrenal tissue could be seen at autopsy examination and if the blood corticosterone levels were significantly lower than in the nonadrenalectomized rats.

Analyses. Rats were weighed daily to determine the increase in total body weight. Immediately after sacrifice, the small intestines were gently flushed with cold saline and weighed. In rats in which only homogenate intestinal enzyme activity and nucleic acids and proteins were to be measured, the small intestines were homogenized 1:5 (intestinal weight:volume of buffer) in 10 mM sodium phosphate buffer, pH 6.0, 0.002% Triton X-100 for biochemical analyses. Fresh homogenate was precipitated in 0.4 N perchloric acid (1:3 v:v) for protein assay.

Disaccharidase activities were assayed at 37° C in 250 μl reaction volume in 50 mM sodium phosphate buffer, pH 6.0, using 0.04 M sucrose (for sucrase activity), 0.0156 M maltose (glucoamylase activity), and 0.0156 M cellobiose or 0.188 M lactose for measuring of lactase activity as described by Tsuboi *et al.* (9). Disaccharidase activity was expressed as mmol substrate per min per total small intestine (total enzyme activity). Specific activity was expressed as total enzyme activity per milligram of protein or per milligram of DNA. Protein was measured by the method of Lowry *et al.* (10). DNA was measured by the method of Burton (11) and RNA as described by Munro and Fleck (12). Corticosterone radioimmunoassay was done as described by the manufacturers of the corticosterone ^{3}H kit (13). For the brush border membrane preparation and protein synthesis studies, an aliquot of the 1:5 (w:v) homogenate was diluted 1:20 (v:v). Brush border membranes were then prepared by the calcium chloride precipitation technique of Schmitz *et al.* (14) without the gradient centrifugation steps. Only membranes with a 5-fold or greater increase in lactase-specific activity per mg of protein from intestinal homogenate to brush border membrane were used for the protein synthesis studies. ^{3}H-leucine incorporation was measured using liquid scintillation counting of cpm homogenate and brush border membrane protein precipitated by 0.4 N PCA. DNA synthesis was measured by the method of Johnson and Guthrie (15). Enterocyte turnover was measured as described by Tsuboi *et al.* (16). Statistical analyses were done using a one-way analysis of variance as an overall comparison of all groups (prostacyclin, hydrocortisone-, or saline-treated). Individual comparisons were made by either the least significant differences procedure in the animals comparing prostacyclin, hydrocortisone or saline treatment and Student's *t* test in the studies where 16,16-DMPGE$_2$ was compared to Triacitin treatment.

Table 1. *Wt changes for rat littermates given parenteral prostacyclin, hydrocortisone, or saline ($\bar{x} \pm SD$)*

Treatment	Animal wt (g) 10 days old ($n = 6$)	14 days old ($n = 6$)
PGI_2	18.1 ± 0.7	21.8 ± 1.2*
Hydrocortisone	17.1 ± 0.8	20.0 ± 1.4†
Saline	17.9 ± 0.8	24.0 ± 1.3

p values *vs* saline control group: * $p < 0.02$; † $p < 0.001$.

RESULTS

Representative weight changes for the suckling rat littermates that were given prostacyclin, hydrocortisone, or saline subcutaneously are shown in Table 1. The animals given hydrocortisone or prostacyclin showed a slower growth rate than did either the

Table 3. *Comparison of small intestinal disaccharide activities after parenteral prostacyclin or hydrocortisone treatment in suckling rats (μmol/substrate utilized/min; $\bar{x} \pm SD$)*

	Treatment PGI_2	Hydrocortisone	Control (saline)
Total lactase	1.62 ± 0.33* (6)	0.94 ± 0.22 (6)	1.07 ± 0.09 (4)
Lactase per mg protein	0.023 ± 0.003† (6)	0.014 ± 0.002 (6)	0.015 ± 0.002 (4)
Lactase per mg DNA	0.517 ± 0.062‡ (9)	0.626 ± 0.0141‡ (9)	0.311 ± 0.06 (10)
Total sucrase	0.48 ± 0.24† (6)	2.98 ± 0.24‡ (6)	0.04 ± 0.02 (4)
Sucrase per mg protein	0.008 ± 0.004* (6)	0.045 ± 0.005‡ (6)	0.001 ± 0.001 (4)
Sucrase per mg DNA	0.118 ± 0.091† (9)	1.040 ± 0.330‡ (9)	0.015 ± 0.032 (10)
Total maltase	5.0 ± 1.9‡ (6)	19.9 ± 3.7‡ (6)	0.7 ± 0.5 (6)
Maltase per mg protein	0.074 ± 0.032† (6)	0.297 ± 0.020‡ (6)	0.010 ± 0.007 (6)
Maltase per mg DNA	1.45 ± 0.33‡ (6)	11.08 ± 4.20‡ (9)	0.48 ± 0.37 (10)

Numbers in parentheses indicates number of rats.
P values *vs* saline control group: * $p < 0.02$; † $p < 0.01$; ‡ $p < 0.001$.

Table 2. *Total small intestinal variables in rats given parenteral prostacyclin, hydrocortisone, or saline ($\bar{x} \pm SD$)*

Treatment	Total small intestine Protein (mg)	DNA (mg)	RNA (mg)	RNA/DNA	^{3}H-thymidine incorporation into small intestinal homogenate (^{3}H cpm/mg DNA)	^{3}H-leucine incorporation into brush border membrane protein (cpm/mg membrane protein) / (cpm/mg total intestine protein)
PGI_2	83 ± 20 (28)	12.0 ± 1.3 (11)	4.03 ± 0.49 (11)	0.34 ± 0.03† (11)	14517 ± 15087 (7)	2.26 ± 0.60† (12)
Hydrocortisone	84.0 ± 24 (30)	11.5 ± 1.4* (12)	4.69 ± 0.56‡ (12)	0.41 ± 0.03‡ (12)	13947 ± 9318 (7)	2.34 ± 0.49† (12)
Control (saline)	87 ± 20 (29)	13.0 ± 1.4 (12)	3.90 ± 0.35 (12)	0.30 ± 0.02 (12)	7454 ± 2342 (8)	1.80 ± 0.24 (12)

Numbers in parentheses indicate numbers of rats.
P values *vs* saline control group: * $p < 0.05$; † $p < 0.025$; ‡ $p < 0.001$.

saline-administered animals or animals not injected with drug or saline. No diarrhea was noticed in any group of animals. Table 2 shows that total small intestinal protein did not differ significantly among the groups of animals receiving prostacyclin, hydrocortisone, or saline. Total DNA per small intestine was slightly lower in the hydrocortisone-treated group. Total RNA was significantly higher in the hydrocortisone-treated group. The RNA:DNA ratio was elevated in the PGI_2- and hydrocortisone-treated groups. No significant differences were seen in DNA synthesis as measured by ^{3}H-thymidine incorporation into DNA of the prostacyclin-treated, hydrocortisone-treated, or control animals. ^{3}H-leucine incorporation as a measure of brush border membrane protein synthesis was normalized to ^{3}H-leucine incorporation into total intestinal homogenate protein. The PGI_2 and hydrocortisone treated animals had a higher ^{3}H-leucine incorporation which reflects greater brush border membrane protein synthesis in PGI_2 and hydrocortisone treated animals. Table 3 demonstrates significant elevations in the activities of sucrase and maltase with mild elevations in lactase after hydrocortisone or PGI_2 administration. Table 4 compares cell turnover times after prostacyclin or hydrocortisone treatment. The rate of cell turnover from crypt to villus tip in the hydrocortisone-administered animals was accelerated. By 72 h, the radiolabeled enterocytes of the hydrocortisone-treated animals were already coming off the tip of the vilus, whereas in the prostacyclin-treated and control rats a level of only about 40–60% of villus height had been reached at 72 h.

Table 4. *Enterocyte turnover after parenteral hydrocortisone or prostacyclin treatment**

Migration (hr)	Treatment: Control (% villus height migrated by ^{3}H-labeled enterocyte)	PGI_2	Hydrocortisone
18	20	20	30
36	30	20	50
72	40	60	>100

* There were two rats in each group.

Table 5 shows the effects of enterally administered 16,16-$DMPGE_2$ on small intestine disaccharidase activities in nonoperated animals. The animals treated with 16,16-$DMPGE_2$ had elevations of total sucrase and specific activity of sucrase per mg of protein. Maltase total units, specific activity per mg of protein and specific activity per mg of DNA were also high in prostaglandin-treated rats. Table 6 shows the effects of enteral 16,16-$DMPGE_2$ treatment on adrenalectomized and sham-operated animals. Blood corticosterone levels were significantly lower in the adrenalectomized rats when compared to the sham-operated rats. No differences were seen within the sham or adrenalectomized groups given prostaglandin or Triacitin. The sham-operated animals showed significant increases of total units of sucrase per mg of protein in addition to increases in maltase total units and maltase-specific activity per mg of protein. Similarly, adrenalectomized animals had significant elevations of sucrase total units and sucrase specific activity per mg of protein. In addition to significant elevations of maltase total units, there were slight increases of maltase-specific activity per mg of protein in the adrenalectomized prostaglandin-treated animals versus adrenalectomized control animals treated only with Triacitin.

DISCUSSION

Several alterations in small intestine characteristics of suckling rats appear to be caused by PGI_2 or hydrocortisone treatment. These include a slower growth rate, elevated RNA/DNA ratios, increased ^{3}H-leucine incorporation into brush border membrane protein normalized to total homogenate protein, and increased disaccharidase activities. The increase in RNA/DNA ratio after glucocorticoid and PGI_2 administration is difficult to interpret

Table 5. *Effects of enterally administered 16,16-$DMPGE_2$ (100 μg/kg) on small intestine disaccharidase activities in nonoperated rats; rats were sacrificed on day 14 of life ($\bar{x} \pm SD$)*

Treatment	Sucrase*: Total units	Sucrase: Specific activity per mg protein	Sucrase: Specific activity per mg DNA	Maltase: Total units	Maltase: Specific activity per mg protein	Maltase: Specific activity per mg DNA
16,16-$DMPGE_2$	0.71 ± 0.42	0.005 ± 0.003	0.253 ± 0.380	7.9 ± 1.8	0.055 ± 0.010	10.5 ± 2.2
Triacitin	0.0	0.0	0.0	3.9 ± 0.8	0.034 ± 0.003	4.9 ± 0.4
p value	<0.01	<0.005	NS	<0.005	<0.005	<0.005

* Degrees of freedom were 8 except for sucrase specific activity/mg DNA where degrees of freedom were 7.

Table 6. *Blood corticosterone levels and disaccharidase activities in sham-operated and adrenalectomized suckling rats after enteral 16,16-$DMPGE_2$ vs vehicle administration; rats were sacrificed on day 15 of life ($\bar{X} \pm SD$)*

Treatment	Corticosterone (ng/ml)	Sucrase: Total units	Sucrase: Specific activity per mg protein	Maltase: Total units	Maltase: Specific activity per mg protein
Sham PGE (4)	30.80 ± 16.57	6.8 ± 2.5*	0.040 ± 0.020†	22.8 ± 5.2*	0.135 ± 0.050
Sham Triacitin (4)	38.48 ± 28.36	2.3 ± 1.4	0.017 ± 0.014	7.1 ± 3.5	0.046 ± 0.009
Adrenalectomized PGE (5)	5.36 ± 4.05	1.8 ± 1.6†	0.015 ± 0.014*	7.1 ± 4.1	0.055 ± 0.030
Adrenalectomized Triacitin (7)	3.31 ± 3.36	0.5 ± 0.2	0.004 ± 0.001	4.3 ± 1.2	0.037 ± 0.060§

Numbers in parentheses indicate numbers of rats.

The mean ± SD corticosterone levels for the sham-operated animals was 34.64 ± 21.89, and for the adrenalectomized animals was 4.16 ± 3.64 ($p < 0.001$ by two-tailed t test). No significant differences were seen in corticosterone levels between animals given PGE or Triacitin within the adrenalectomized or sham-operated groups.

p, values for PGE groups versus respective triacitin control groups) * $p < 0.01$; † $p < 0.05$; ‡ $p < 0.025$; § $p = 0.009$.

but may be related to increased protein synthesis, which is supported by the increased ^{3}H-leucine incorporation into brush border membrane protein. When 16,16-DMPGE$_2$ was administered enterally, sucrase and maltase activities were increased in intact sham-operated and adrenalectomized rats suggesting that the adrenal-intestinal axis is not necessary for this effect.

The effects of glucocorticoids on small intestine in developing mammals have been described in numerous investigations (2, 4, 5, 17–21). These effects are thought to be associated with biochemical maturation of the absorptive capabilities of mammalian small intestine which are dependent on disaccharidase activities. A glucocorticoid-sensitive period has been described for jejunal sucrase in rats that occurs just before and coincident with the appearance of the enzyme (14–17 days) (22). Data from previous investigations have suggested that similar effects may follow subcutaneous administration of PGI$_2$ or subcutaneous implantation of 16,16-DMPGE$_2$ minipumps (7). Similar effects also have been seen after enteral administration of 16,16-DMPGE$_2$ by gavage to suckling but not adult rats (8).

In adult rats, prostaglandins are known to influence many aspects of gastrointestinal function, including motility, secretion, mucosal blood flow, mucus production, and ulcer formation (23). Both PGE$_2$ and lesser amounts of prostaglandin F are present in the gastrointestinal tract (24). PGI$_2$ is also found in the rat stomach (25). It has gastric antisecretory and cytoprotective properties similar to those of PGE$_2$ (26). Robert *et al.* (26, 27) have shown that prostaglandins may have a "cytoprotective" effect on the gastrointestinal tract and speculate that they may protect the small intestinal mucosa from luminal insults by regulating mucus secretion. Lichtenberger *et al.* (28) have demonstrated that this protective effect may be partially related to an increased surfactant-like material coating the surface of the intestinal tract.

Since exogenously administered prostaglandins cause somewhat similar effects to those of the glucocorticoids, it is apparent from our studies that these compounds may also relate to small intestinal metabolic processes during development. Our data suggest that the disaccharidase stimulatory effect is not dependent on the presence of the adrenal glands, and therefore the prostaglandins do not act through the adrenal-intestinal axis. Several possibilities could explain the mechanism of the prostaglandin stimulation effect on the disaccharidases. Another "second messenger," such as cyclic AMP (29), could be an important mediator of this prostaglandin-initiated stimulation of disaccharidase activities. On the other hand, this stimulation could be a direct effect of the prostaglandins themselves. Another possibility is that the positive surfactant barrier secreted by the enterocyte in response to prostaglandin administration (28) may protect these brush border membrane-bound enzymes from proteolysis by luminal proteases. These are known to hydrolyze intestinal brush border disaccharidases as demonstrated in previous studies in pancreatic-deficient animals (30). Further studies are required to elucidate the mechanism of this prostaglandin-initiated stimulation of disaccharidase activity in the mammalian small intestine.

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