Stimulation of ornithine decarboxylase activity in digestive tract mucosa

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JAIN, RAJEEV, BARBARA E. EIKENBURG, AND LEONARD R. JOHNSON. *Activation of ornithine decarboxylase in digestive tract mucosa.* Am. J. Physiol. 253 (Gastrointest. Liver Physiol. 16): G303–G307, 1987.—Refeeding fasted rats with normal rat food and with a variety of amino acids increases ornithine decarboxylase (ODC) activity considerably. The time course of that increase, the areas of the digestive tract directly affected, and the effective concentrations of stimulants are unknown. By use of isolated 5-cm segments of rat jejunum, we determined that maximal activation of ODC occurred after a 2-h exposure to 0.6 M glycine. Increased activity was first apparent after a 1-h exposure to glycine and was significant after a 2-h exposure to 0.05 M glycine. ODC activity increased the most in segments of jejunum, followed by segments of ileum and then duodenum. Glycine (0.4 M) failed to increase ODC activity in gastric and colonic mucosa. Interestingly, D-alanine was more effective than L-alanine in stimulating ODC activity in the jejunum. Enzyme activity was not dependent on osmotic activity of the test substances. Glucose increased enzyme activity, but mannitol and fructose were without effect. The effects of glycine were significantly greater than those of glucose. In summary, ODC of the small intestinal mucosa is increased by direct contact with amino acids and glucose within 2 h after exposure. Increased enzyme activity depends on the nature of the stimulant rather than the osmotic activity of the solution in contact with the mucosa.

mucosal growth; polyamines; sugars; amino acids; small intestine; absorption

THE POLYAMINES, spermidine and spermine and their precursor putrescine, are found in virtually all cells of higher eucaryotes (15). The exact function of the polyamines at the molecular level has not been elucidated, but they are intimately involved in the regulation of cell growth, and their concentrations are highly regulated. Recent studies have shown that both normal and abnormal cell growth and differentiation require polyamines (7, 15). Polyamine synthesis is closely regulated by changes in the cellular activities of the enzymes ornithine decarboxylase (ODC; EC 4.1.1.17) and *S*-adenosylmethionine decarboxylase (EC 4.1.1.50). ODC is the initial rate-controlling enzyme in the pathway, and in normal tissue its activity is quite low. An increase in ODC activity is one of the earliest events associated with cellular proliferation (15, 20).

The basal activity of ODC in the mucosa of the small intestine is high compared with most tissues (1); however, it still increases dramatically in response to feeding. Moore and Swendseid (13), for example, reported 40-fold increases in enzyme activity 1 h after fasted rats were given an amino acid mixture by gavage. In our laboratory, refeeding fasted rats increased jejunal ODC activity from 8.8 to 308 pmol $^{14}CO_2 \cdot h^{-1} \cdot mg\ protein^{-1}$ 2 h after the start of the meal (24) and produced 15-fold increases in ileal mucosal ODC activity (23). Fasting itself decreases activity to ~20% of that found in fed animals (23); ODC activity in rat small bowel mucosa also increases after partial resection (9), during lactation (25), during the third week of life at the time of weaning (10), and after luminal obstruction (17). Each of these examples is associated with either increased food intake or increased exposure of a portion of the gut to luminal contents (resection and obstruction); each is also associated with increased mucosal growth.

The ingestion and physical and chemical presence of food within the digestive tract provide many stimuli that result in mucosal growth (8) and could also trigger increases in ODC activity. These stimuli can be more or less divided into humoral fractions (hormones, absorbed nutrients) and luminal factors (nutrients, chemicals, secretions). By use of rats with jejunal Thiry-Vella loops we have shown that direct infusion of gut contents into the loop activates ODC 10-fold in loop mucosa without increasing enzyme activity in the intact segment of bowel (24). Refeeding the fasted animal increased ODC activity 4-fold in the loop but caused a 35-fold increase in enzyme activity in the intact bowel. These findings indicate that the large majority of stimulation of enzyme activity is due to luminal factors.

The purpose of the current study is to define some of the characteristics of the local activation of ODC. By use of isolated 5-cm segments of jejunum we have determined the optimal concentration of glycine needed for activation, the time the mucosa must be exposed to the stimulant, and the role of osmotic pressure in activating the enzyme. We have also determined which portions of the digestive tract mucosa respond to direct exposure to glycine with increased ODC activity.

METHODS

Animals. Male Sprague-Dawley rats weighing 125–150 g were housed in wire-bottomed cages with Purina laboratory chow and water available ad libitum. Food, but not water, was removed 48 h before surgery.

The rats were anesthetized with ether and the peritoneal cavity was opened via a midline incision. Two or three consecutive segments of the small intestine or

proximal colon were isolated by ligation. Small bowel segments were 5 cm long, whereas colonic segments were 3 cm in length. In most studies, jejunal segments 20–35 cm distal from the pylorus were used. In one experiment the stomach was isolated by pylorus ligation, or segments of duodenum, ileum, or colon were used. The two duodenal segments began at the pylorus and were produced by ligatures 5 and 10 cm distally. Ileal segments began 3 cm proximal to the ileocecal junction and additional ligatures were placed at 8, 13, and 11 cm proximally to create three segments. Colonic segments began 2 cm distal from the ileocecal junction and were made by placing additional ligatures 5, 8, and 11 cm farther down the colon. No animal had more than three segments, and these were confined to one area of the tract.

In a typical experiment, 0.5 ml of saline (control) or a test solution was injected into each segment using a 1-ml syringe. The midline incision was then closed, and the animals were allowed to recover in individual cages without food or water. Two hours after injecting the test substances the rats were killed by an overdose of ether and exsanguinated. All animals were killed between 11 and 12 P.M.

The individual segments were isolated, removed, opened, and rinsed in ice-cold saline. Mucosa from these tissues was obtained by scraping with a glass slide over an ice-cold glass plate. ODC activity was then measured in the mucosal scrapings.

Experimental design and protocols. The time course for the activation of ODC was determined in the first study. Each rat was prepared with two jejunal segments. One segment was injected with saline and the other with 0.8 M glycine. Rats were killed 15, 30, 60, 120, and 240 min later. Six animals were studied at each time point. In three of these, saline was injected into the proximal segment and glycine into the distal. The order was reversed in the remaining three rats.

The optimal concentration of glycine for ODC activation was determined in the second study. Saline or two concentrations of glycine were injected into each of three segments of jejunum, and the animals were killed 2 h later. Glycine was injected at concentrations of 0.05, 0.2, 0.4, 0.6, and 0.8 M. Each dose of glycine was administered to six rats.

The ability of glycine to increase ODC activity in different areas of the gastrointestinal tract was examined in the third study. Either saline or 0.4 M glycine was injected into the stomach of six rats, or saline and 0.4 M glycine were injected into six rats prepared with two duodenal, jejunal, ileal, or colonic segments. The animals were killed 2 h later.

The abilities of D- and L-amino acids to increase ODC activity were examined using two concentrations of D- and L-alanine. Rats were prepared with three jejunal segments, and saline, 0.1 M L-alanine, or 0.1 M D-alanine was injected into each segment. In the second set of eight rats, 0.4 M doses of alanine were used. Animals were killed 2 h after exposure to the amino acids.

The role of osmotic concentration in the activation of ODC was examined in the final experiment. Rats were prepared with three jejunal segments. In this series of studies 0.15 M NaCl (saline) was always injected into one of the three segments. The other two segments were injected with either water, (in M) 0.4 mannitol, 0.4 fructose, 0.4 glucose, 0.8 glucose, 0.15 NaCl plus 0.1 glycine (total 0.4 osmol), or 0.4 NaCl. Each test substance was injected into six rats.

ODC assay. Mucosal scrapings were weighed and divided into two portions. One portion was used to measure protein content by the Bradford (3) method. ODC activity was assayed by a radiometric technique in which the amount of $^{14}CO_2$ liberated from DL-[1-^{14}C]ornithine (51.3 mCi/nmol, New England Nuclear, Boston, MA) was estimated. Intestinal mucosa was collected and placed in 0.067 M sodium-potassium phosphate buffer, pH 7.4, containing 0.02% lauryl ether, 5 mM NaF, 100 μM pyridoxal phosphate, 10 μM ethylenediaminetetraacetic acid (EDTA), and 2 mM dithiothreitol. The tissues were homogenized, sonicated, and centrifuged at 30,000 *g* for 25 min. An aliquot from the 30,000 *g* supernatant was incubated in stoppered vials in the presence of ~2 pmol of [^{14}C]ornithine for 15 min at 37°C. The $^{14}CO_2$ liberated by the decarboxylation of ornithine was trapped on a

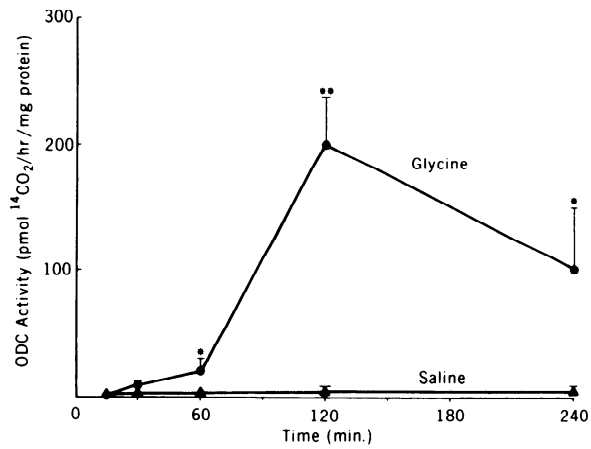

FIG. 1. Ornithine decarboxylase (ODC) activity in mucosa of 5-cm jejunal segments exposed to 0.8 M glycine or saline or different lengths of time. Glycine was injected into segments at *time 0*, and rats were killed at various times afterward as indicated on *abscissa*. Each *point* represents mean and SE of data for 6 rats. * $P < 0.05$ compared with segments exposed to saline for same time. ** $P < 0.01$ compared with saline.

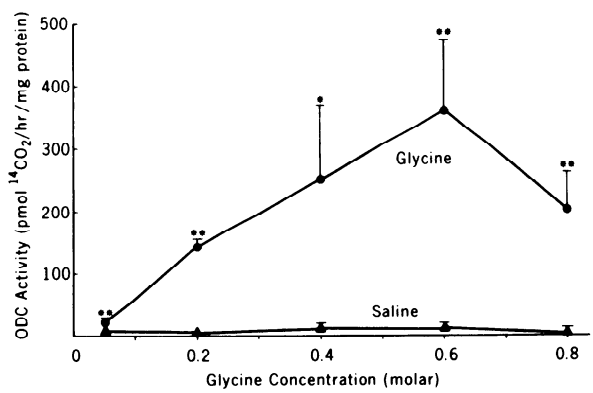

FIG. 2. Ornithine decarboxylase (ODC) activity in mucosa of 5-cm jejunal exposed segments to different concentrations of glycine as shown on *abscissa* or to saline for 2 h. Each point shows mean and SE of data from 6 rats. * $P < 0.05$ compared with saline. ** $P < 0.01$ compared with saline.

piece of filter paper impregnated with 20 μl of 2 N NaOH and suspended in a centerwell above the reaction mixture. The reaction was stopped by the addition of trichloroacetic acid to a final concentration of 10%. The $^{14}CO_2$ trapped in the filter paper was measured by liquid scintillation spectroscopy at a counting efficiency of 99%. Blanks were run simultaneously by using a vehicle instead of the supernatant. Results are expressed picomoles $^{14}CO_2$ per milligram protein per hour.

Statistics. Results are expressed as means ± SE. The significance of the difference between means was established by analysis of variance. The level of significance was determined using the Duncan's multiple-range test (22).

RESULTS

In the jejunal mucosa, ODC activity increased significantly within 1 h of being exposed to 0.8 M glycine (Fig. 1). Activity peaked after 2 h and declined after 4 h. In the remaining experiments all rats were killed after a 2-h exposure to the test solution injected into the segment.

Figure 2 illustrates the activation of jejunal ODC as a function of the concentration of glycine. ODC activity increased significantly in response to as little as 0.05 M glycine. Activity peaked in response to 0.6 M glycine and represented a 35-fold increase in enzyme activity compared with segments exposed to saline in the same rats.

In fasted animals the highest levels of enzyme activity were found in the jejunum. This area of the gut also exhibited the highest level of stimulated ODC activity (Fig. 3). Glycine also significantly increased enzyme activity in the mucosa of segments of ileum and duodenum but not in the stomach or segments of proximal colon (Fig. 3).

Somewhat surprisingly, D-alanine increased ODC activity more potently than L-alanine (Fig. 4). Compared with the saline control, 0.1 M L-alanine had no effect, whereas 0.1 M D-alanine increased ODC activity approximately eight-fold. Increasing the concentration of L-alanine to 0.4 M enhanced ODC activity to a level comparable to that stimulated by 0.1 M D-alanine. The effect of 0.4 M D-alanine was twice that of an equal concentration of L-alanine.

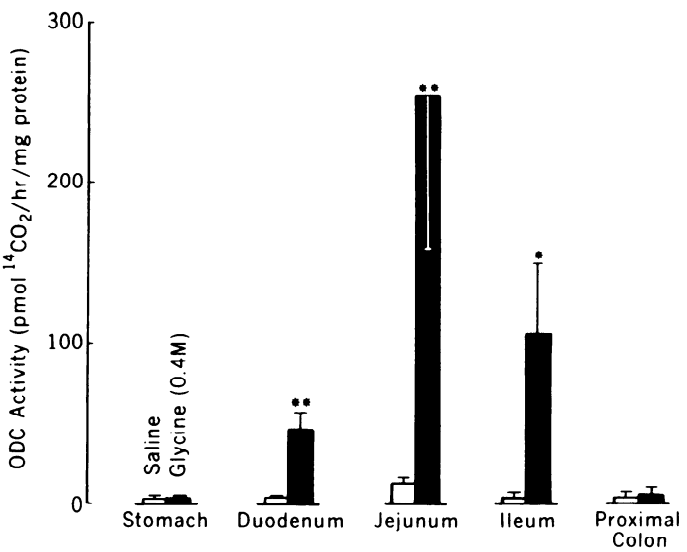

FIG. 3. Ornithine decarboxylase (ODC) activity in various portions of digestive tract 2 h after being exposed to 0.4 M glycine or saline. *Bars* indicate means and SE of observations in 6 rats. * $P < 0.05$ compared with saline. ** $P < 0.01$ compared with saline.

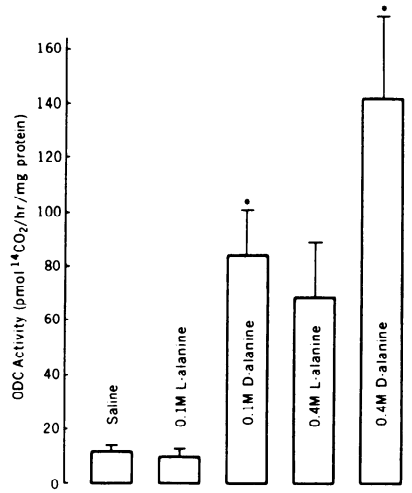

FIG. 4. Ornithine decarboxylase (ODC) activity in jejunal mucosa 2 h after exposure to saline or 0.1 M L- or D-alanine, or 0.4 M L- or D-alanine. Data are means and SE of measurements in 8 rats. * $P < 0.05$ compared with same dose of L-alanine.

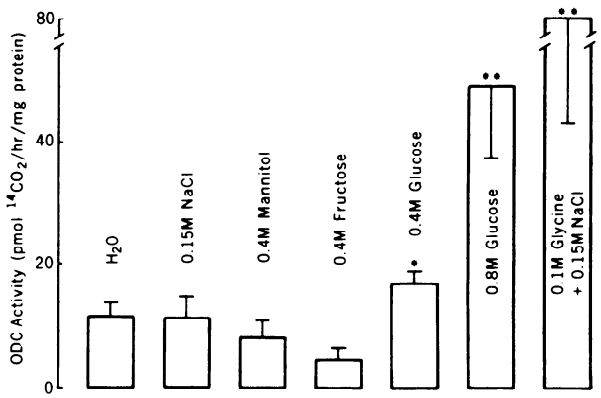

FIG. 5. Ornithine decarboxylase (ODC) activity of jejunal mucosa 2 h after exposure to water, (in M) 0.15 NaCl, 0.4 mannitol, 0.4 fructose, 0.4 fructose, 0.4 glucose, 0.8 glucose, or 0.1 glycine in 0.15 NaCl. Data shown are means and SE for 6 measurements. * $P < 0.05$ compared with mannitol or fructose. ** $P < 0.01$ compared with water.

As shown in Fig. 5, exposure of jejunal mucosa to water or saline resulted in nearly equal levels of ODC activity. Glucose, 0.4 M, significantly increased ODC activity compared with either 0.4 M mannitol or 0.4 M fructose. Neither of these latter substances increased ODC activity over control levels. Doubling the concentration of glucose to 0.8 M resulted in a highly significant stimulation of ODC activity approximately fourfold higher than control. Increasing the concentration of NaCl to 0.4 M (0.8 osmol) had about the same effect as 0.4 M glucose, and the increase was significantly different from control (data not shown). The addition of glycine to 0.15 M NaCl to a final amino acid concentration of 0.1 M (total 0.4 osmol) was approximately twice as effective as 0.8 M glucose (Fig. 5).

DISCUSSION

After a meal, mucosal ODC activity is elevated by both hormonal and direct mucosal stimulation by dietary con-

stituents (24). Several studies have attempted to examine the characteristics of ODC activation by luminal constituents (6, 12, 13). Fugimoto et al. (6) found that ODC peaked in intestinal mucosa 4 h after fasted rats had begun to eat. Moore and Swendseid (13) administered an amino acid mix, patterned after casein, to fasted rats by gastric intubation. ODC activity increased substantially in the small intestine after only 1 h and peaked by 1.5 h. Minami et al. (12) administered casein or single amino acids by gavage and showed that ODC activity peaked 4 h later in the entire small intestine. Obviously the time the mucosa in the above studies was first exposed to the various nutrients and the amount of exposure were impossible to determine. Both of these variables were dependent on gastric emptying, intestinal motility, and in some cases the time necessary for and the completeness of digestion.

Our own results show that direct exposure of jejunal mucosa to glycine significantly increases ODC activity after 1 h and that peak activity occurs by 2 h. Interestingly Moore and Swendseid (13) showed a more rapid activation than we did, even though they administered amino acids by gastric intubation. They measured ODC activity in the proximal 15 cm of small intestine, and some time must have been required for the nutrients to empty from the stomach and come into contact with the intestinal mucosa. However, their results could also have been due to hormone release from the stomach or proximal bowel and the interaction of humoral stimulants with the nutrients to result in a more rapid activation of the enzyme. Both gastrin and cholecystokinin have been shown to greatly enhance the effect of casein in activating intestinal ODC (6). A similar phenomenon has also been reported for insulin and a number of growth factors in a variety of cultured cell lines. Rinehart and Canellakis (16) found that nerve growth factor, epidermal growth factor, and platelet-derived growth factor as well as insulin failed to induce ODC activity in pheochromocytoma (PC 12) cells, fibroblasts (NIH 3T3), or hepatoma (KRC-7) cells unless a minimal concentration of "an ODC inducing amino acid" was present. Considering the short length of intestine (5 cm) exposed to the amino acid in our study it seems unlikely that sufficient amounts of a humoral factor were released to influence the results.

We chose glycine as a test substance for a number of reasons. First, it's a common amino acid that is readily transported by active mechanisms. Second, Minami et al. (12) have shown that it was a potent inducer of ODC activity compared with most other amino acids when administered by gavage. Third, we were able to obtain extremely reproducible results with it in preliminary studies. Figure 2 shows that small amounts of glycine resulted in significant activation of ODC. In our system peak activation occurred with 0.5 ml of 0.6 M glycine. This amounts to only 0.3 mmol glycine/5-cm segment of jejunum. Significant activation was produced by 0.05 M solution amounting to only 0.025 mmol/segment.

By use of 0.4 M glycine as a test solution, we examined which portions of the digestive tract were able to increase ODC activity in response to topical stimulation. This is the only study, to our knowledge, that has controlled the amount of stimulating agent reaching each part of the tract. After a normal meal almost all nutrients are absorbed before they leave the jejunum. In the current study glycine had no effect on gastric mucosal ODC activity, which agrees with previous results demonstrating that ODC activity of the gastric mucosa is not induced by a meal (23). We found increased ODC activity throughout the small intestine, although the activity of the enzyme increased the most in the jejunum. This pattern (Fig. 3) of enzyme activation is similar to the distribution of the mechanisms for active amino acid transport in the small intestine (14). Refeeding fasted rats has been reported to have no effect (11) or to stimulate ODC activity of colonic mucosa severalfold (21, 23). In our study, topical glycine had no effect on colonic mucosal ODC. In general, colonic epithelia do not absorb amino acids (2, 4). It is likely that the activation of colonic mucosal ODC after a meal (21, 23) is due to humoral factors or other luminal stimulants such as amines (17, 18, 24).

The ability of amino acids to directly increase ODC activity is not limited to the L-forms that occur naturally in animal and plant protein. We found that D-alanine was actually more potent than L-alanine as a stimulant of ODC activity. Previously Minami et al. (12) had fed rats D- and L-amino acids and found that the D-forms of alanine and serine were just as effective as the L-forms. However, because of the design of the study it was impossible to determine whether ODC activation was due to direct effects of the amino acids, hormones, nerve stimulation, or a combination. Our results indicate that D-alanine directly activates ODC. Even though D-amino acids are not metabolized in mammalian systems, they are often actively transported by gut epithelia. D-Alanine is transported about one-tenth as rapidly as the L-form by the neutral amino acid carrier of rat jejunum (14). However, D-alanine is transported by the amino acid carrier to about the same extent as L-alanine (14). Currently we have no explanation for the greater effect of D-alanine on ODC activity compared with L-alanine.

The activation of jejunal ODC does not depend on the osmotic activity of the solution in contact with the mucosa. Compared with water, 0.15 M NaCl, 0.4 M mannitol, and 0.4 M fructose were without effect (Fig. 5). Actively transported glucose, however, increased enzyme activity at the 0.4 M dose, indicating that actively transported substances are capable of stimulating the enzyme. Fructose transport is carrier mediated, but it is not active. Glucose was not nearly as potent as glycine in stimulating the enzyme. In fact, 0.1 M glycine in saline resulted in enzyme levels four times higher than the same osmolar (0.4 osmol) concentration of glucose and twice those in response to 0.8 M glucose. NaCl at 0.8 osmol had about half the effect of 0.8 M glucose. It was apparent that glycine and alanine were much more potent activators of the enzyme than glucose. However, glucose also increased enzyme activity to a greater extent than identical osmolar concentrations of NaCl. Collectively these data indicate that in order to increase ODC activity the solute must be actively transported.

In conclusion, ODC activity of the small intestinal

mucosa is increased by direct contact with the amino acids, glycine and alanine, and by glucose and hypertonic NaCl within 2 h after exposure. The pattern of ODC increases in the various regions of the gut as evoked by glycine follows the known capacities of the different regions for the active absorption of amino acids. Whether or not a particular compound increases ODC may depend on whether it is actively transported.

It is tempting to speculate that nutrient-stimulated mucosal ODC activity then leads to mucosal growth. However, there are a number of problems with this hypothesis that must be solved before doing so. First, the enzyme ODC is located in the villous tip cells not the dividing crypt cells (5). Second, putrescine levels increase dramatically in the crypt cells after refeeding (5). Third, difluoromethylornithine, a specific and irreversible inhibitor of ODC, blocks growth of the gastric mucosa after refeeding even though there is no increase in ODC in this tissue (23). Fourth, difluoromethylornithine blocks the trophic effects of gastrin, a growth factor that does not increase ODC (19). These findings all indicate that increased ODC activity per se is not the stimulus for growth and suggest that increases in growth may be related more closely to actual polyamine levels.

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