The Influence of Estradiol and Diet on Small Intestinal Glucose Transport in Ovariectomized Rats

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Although gender differences exist for intestinal absorption of nutrients and drugs, the possible role estradiol may play in modulating nutrient transport has not been established. Therefore, small intestine glucose transport was measured 1 week after administering estradiol to ovariectomized rats fed diets high in carbohydrate (C) or protein (P). Rats treated with estradiol ate 21% less ($P < 0.05$) and lost body mass (7%; $P < 0.05$) but did not have smaller intestines. Administration of estradiol increased rates of glucose transport, but only when the rats were fed the C diet. These findings indicate that estradiol causes a disconnect between food intake and the dimensions and nutrient transport capacities of the small intestine. Furthermore, the responses to estradiol are influenced by diet composition, are not of the same magnitude for rats and dogs, and can be predicted to affect systemic availability of nutrients and drugs. Exp Biol Med 229:227–234, 2004

Key words: rat; estradiol; diet; glucose transport; intestine

The cells lining the gastrointestinal tract (GIT) are exposed to and respond to regulatory signals that originate from several sources. It is well established that the abundances of hydrolases and transporters in the brush-border membrane (BBM) are modulated to match changes in the composition of lumenal contents, hence dietary inputs. For example, switching laboratory mice among diets with varying levels of protein and carbohydrate has revealed a direct relationship between rates of carrier-mediated glucose and amino acid uptake and diet composition (1). However, the increased rates of nutrient absorption after caloric restriction and short-term starvation (2–5) provide evidence that enterocyte functions are also modulated by signals other than lumenal nutrient concentrations.

The basolateral membrane of enterocytes has receptors for cholecystokinin, gastrin, and other regulatory peptides associated with the GIT, which are known to modulate enterocyte absorption of ions (6–9) and carrier-mediated uptake of glucose by the sodium-dependent transporter SGLT-1 (10–14). Less is known about the responses to signaling molecules that originate from sources other than the GIT and associated organs. Enterocytes also possess estrogen receptors, with the densities higher in females (15) and varying among regions (16). Administering estradiol to ovariectomized rats increases the activities of small intestinal BBM disaccharidases, peptidases, and alkaline phosphatase (17). Similar responses have been reported after administering synthetic derivatives of gonadal steroids used as contraceptives (18). Estradiol increases rates of small intestine calcium absorption by ovariectomized laboratory rodents (19–22) and postmenopausal women (23) and absorption of magnesium, (24), iron (25), and strontium (21, 26) in animal models and humans. These findings correspond with the improved calcium status after providing estrogen therapy to postmenopausal women and young hypogonadal girls (27). The responses to estradiol correspond with gender-based differences for intestinal calcium absorption (28), colonic functions (29), and amino acid digestibility (30) and may underlay the wider variation in systemic availability exhibited by females for some oral drugs (31–34).

Even though gender differences for estradiol and GIT characteristics are recognized, there is surprisingly little known about whether estradiol modulates the transporters for macronutrients despite the relevance to pharmacokinetics of drugs targeted to nutrient transporters to improve bioavailability. We have previously measured higher rates of carrier-mediated glucose transport by the proximal small intestine of mature, intact, anestrus female dogs after 1 week of receiving estradiol (35). A concurrent increase in the absorption of a synthetic tripeptide coincided with peak

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Table 1. Composition of the Two Experimental Diets Fed to the Rats for 4 Weeks[a]

Ingredient	High carbohydrate (g/kg)	High protein (g/kg)
Casein	200	650
DL-Methionine	3	3
Corn starch	150	150
Sucrose	450	0
Corn oil	50	50
Salt mix S10001[b]	35	35
Vitamin mix V10001[c]	10	10
Choline bitartrate	2	2
Cellulose	100	100

[a] Diets were formulated and prepared by Research Diets, Inc. (New Brunswick, NJ) and were based on the AIN 76A rodent diet (36).
[b] Composition of the salt mixture (amount in 35 g): calcium phosphate dibasic (Ca = 5.2 g; P = 4.0 g), magnesium oxide (Mg = 0.5 g), potassium citrate (K = 3.6 g); potassium sulfate (S = 0.33 g), chromium potassium sulfate (Cr = 2.0 mg), sodium chloride (Na = 1.0 g; Cl = 1.6 g), cupric carbonate (Cu = 6.0 mg), potassium iodate (I = 0.2 mg), ferric citrate (Fe = 45 mg), manganous carbonate (Mn = 59 mg), sodium selenite (Se = 0.16 mg), zinc carbonate
(Zn = 29 mg), with sucrose as the remainder.
[c] Composition of the vitamin mixture (amount in 10 g): vitamin A (1200 μg), vitamin D (25 μg), vitamin E (35 mg), vitamin K (50 μg), biotin (0.2 mg), cyanocobalamin (10 mg), folic acid (2 mg), nicotinic acid (30 mg), calcium pantothenate (16 mg), pyridoxine-HCl (7 mg), riboflavin (6 mg), thiamin HCl (6 mg), with sucrose as the remainder.

systemic availability that was 1000-fold higher and occurred much earlier (5 mins vs. 45–90 mins). The present study addressed two questions: Does estradiol similarly increase rates of nutrient absorption in a rodent model using glucose as the model nutrient? Does the presence or absence of estradiol influence the ability of the intestine to modulate rates of nutrient transport to match changes in diet composition? Rats were selected for comparative purposes because they differ from dogs with respect to estrus cycle frequency and duration, which could influence the pattern and magnitude of responses. Moreover, because of the natural omnivorous diet, rats are able to tolerate wider variation in diet composition than dogs. Additionally, rats are a more economical animal model and are more available to investigators examining the influence of estradiol on gastrointestinal characteristics.

Materials and Methods

Animals and Their Care. All phases of the research involving animals were approved by the Mississippi State University Institutional Animal Care and Use Committee and were done in facilities accredited by the American Association for the Accreditation of Laboratory Animal Care. A total of 25 ovariectomized retired breeder rats of the Sprague-Dawley strain were purchased from a commercial supplier (Charles Rivers Laboratories, Wilmington, MA). The life span of rats is 3 years, and retired breeders are 1–1.5 years of age. Therefore, ovariectomized retired breeders were considered as a more appropriate model for postmenopausal women than the use of young rats that are ovariectomized before reaching sexual maturity. On arrival, the rats were housed (two per cage) in a controlled environment (22°C with 40%–60% relative humidity and lighting from 0700–1900 hr). Food and water were available continuously.

Treatments. The rats were randomly assigned to four treatments. These included two diet groups, each of which was subdivided into animals injected with vehicle or estradiol. The two diets were based on the AIN 76A rodent diet (36), with cellulose added at 100 g/kg; met the energy and nutrient requirements of adult rats; and differed in having ratios for protein relative to digestible carbohydrate that were low (20%:60%; C diet) or high (65%:15%; P diet; Table 1). The use of two diets allowed us to search for a possible interaction between estradiol and diet in regulating rates of glucose transport. The diets were fed for a total of 4 weeks, which included an acclimation period of 3 weeks prior to administering estradiol. This was considered to be long enough to allow for full adaptation to diet composition and to deplete the rats of phytoestrogens, which could influence intestinal nutrient absorption (37) and are present in commercial rodent chows formulated with soy and other plant products.

During the fourth and final week of the feeding period, six of the rats fed the C diet and seven of the rats fed the P diet were given daily subcutaneous injections of estradiol cypionate (20 μg/kg/day of 17β-estradiol equivalent; Pharmacia & Upjohn, Kalamazoo, MI). This dose of estradiol is sufficient to increase calcium absorption by ovariectomized mice (21) and rats (19) and was considered to be a pharmacologic dose. The remaining six rats fed in each diet group received subcutaneous injections of an identical volume of vehicle (sterilized corn oil).

The rats were weighed at the beginning of the fourth week of feeding when the injections of estradiol or vehicle were started. Consumption of feed was recorded during the final week.

Collection of Tissues. The rats were euthanized by carbon dioxide asphyxiation after receiving estradiol or the vehicle for 7 days. After body mass was recorded, a midventral laparatomy was performed. Blood was collected from the inferior vena cava, and the entire postgastric alimentary canal was removed and placed in cold (2°–4°C) mammalian Ringers solution that had been aerated with a mixture of 95% O_2 and 5% CO_2. The small intestine was isolated, the associated mesentery was removed, the lumenal contents were removed by flushing with the Ringers, the total mass of the small intestine was recorded, and the length was measured in a relaxed state on a horizontal surface.

Measurement of Serum Estradiol Concentration. The blood collected at the time of death was centrifuged (3000 *g*; 10 mins) and the serum was stored at –80°C. Estradiol concentrations were measured in duplicate using an enzyme-linked immunoassay and a 17β-estradiol standard (Assay Designs, Inc., Ann Arbor, MI). Based on

Table 2. Body Mass, Food Intake, and Intestinal Dimensions of Ovariectomized Mature Rats Fed Diets High in Carbohydrate and Protein for 4 Weeks and Injected the Last Week with Vehicle or Estradiol[a]

Group	*n*	Initial body mass (g)	Final body mass (g)	Food intake (g/week)[b]	Intestine length (cm)	Intestine mass (g)
High carbohydrate						
Vehicle	6	392 ± 23	389 ± 23	98.4 ± 4.9A	140 ± 2	4.2 ± 0.3
Estradiol	6	411 ± 27	387 ± 23	77.2 ± 2.4B	138 ± 4	4.2 ± 0.5
High protein						
Vehicle	6	373 ± 23	370 ± 23	105.2 ± 3.6A	144 ± 4	5.7 ± 1.0
Estradiol	7	390 ± 21	360 ± 23	85.3 ± 3.0B	143 ± 3	5.2 ± 0.6

[a] Values are means ± SEM.
[b] Values in column not sharing the same letter are significantly different ($P < 0.05$).

preliminary measurements, it was possible to quantify concentrations of estradiol in 100-μl aliquots of undiluted plasma samples.

Measurement of Glucose Transport. Glucose transport was measured using everted sleeves prepared from one segment of small intestine that originated from ~12–20 cm distal to the pyloric sphincter (proximal) and a second segment that extended from ~12–20 cm proximal to the ileocolonic junction (distal). Following an established protocol (38), each segment was everted, and 1-cm sleeves (five for the proximal and two for the distal) were mounted on stainless-steel rods with diameters that approximated those of the tissue sleeves (3–5 mm). The tissues were kept in cold, aerated Ringers. Measurements of transport began 45 mins after death, at which time the tissues were transferred to 37°C Ringers for 4 mins before they were suspended for 2 mins in uptake solutions consisting of 37°C Ringers aerated with the gas mixture, stirred (1200 rpm), and containing unlabeled D-glucose. Rates of glucose transport were quantified by adding tracer concentrations of ^{14}C labeled D-glucose; ^{3}H labeled L-glucose was added to the solution at tracer concentration to correct for D-glucose in the extracellular fluid and passively absorbed. Glucose transport by the proximal small intestine was measured at concentrations (mmol/L) of 0.0016 (tracer alone), 0.4, 2, 10, and 50 mmol/L and in the distal small intestine at 0.0016 and 50 mmol/L. After exposure to the transport solutions, the tissues were rinsed in cold Ringers without glucose for 20 secs, carefully blotted to remove adherent fluid, removed from the rods, and placed in tared vials. Wet mass was recorded, the tissues were solubilized (Solvable; PerkinElmer Life Sciences Inc., Boston, MA), scintillant was added (UltimaGold, PerkinElmer), and the associated radioactivity was quantified by liquid scintillation counting. Rates of transport were calculated and normalized to wet tissue mass and per-centimeter length. Because of the use of L-glucose, which is absorbed passively, independent of carriers, calculated values represent rates of carrier-mediated transport.

The capacity of the entire small intestine to transport glucose was estimated by summing uptake capacities in the proximal and distal regions. The regional capacities were calculated as the product of uptake/cm at 50 mmol/L in each region times regional length (50% of total small intestine length).

Ratios were calculated for the tissue accumulation of tracer concentrations of labeled glucose in the presence and absence of 50 mmol/L unlabeled substrate. These accumulation ratios were used to verify the presence of a saturable component of absorption. Specifically, if a saturable pathway of glucose uptake was present, accumulation of tracer would be reduced by the presence of 50 mmol/L unlabeled glucose due to competition for transporter sites.

Chemicals. The D-[^{14}C (U)]-glucose and L-[1-^{3}H (N)]-glucose were purchased from PerkinElmer. All other chemicals were purchased from Sigma Chemical Company (St. Louis, MO) and were of the highest purity available.

Statistics. Values presented in the figures and tables are means ± SEM. Two-way ANOVA was used to evaluate the main effects of diet and estradiol on body mass, feed consumption, intestinal dimensions, plasma estradiol concentrations, and capacities of the entire small intestine to transport glucose. The PROC MIXED procedure was used to evaluate the main effects of estradiol, diet, and region and their interactions on rates of glucose uptake. A critical value of $P < 0.10$ was accepted as indicative of a main effect. When a significant main effect was detected, differences were identified using Student's t test and $P < 0.05$ as the critical level of significance. The PROC univariate procedure was used to determine if accumulation ratios for glucose uptake were different from a value of 1.0. All statistical analyses were performed using the Statistical Analysis System (Version 8.2; SAS Institute, Cary, NC).

The relationship between rates of glucose transport and glucose concentration was evaluated using nonlinear regression analysis (Enzfitter; Elsevier-Biosoft, Amsterdam, Netherlands) to estimate maximum rates of carrier-mediated uptake (V_{max}) and the apparent affinity constant (K_m). The data were fit to a model equation for a single transporter. Fitting the data to models with two transporters or a single transporter plus a diffusion coefficient did not improve the fit.

Results

Feed Consumption, Body Mass, and Intestinal Dimensions. When normalized to body mass, rats treated

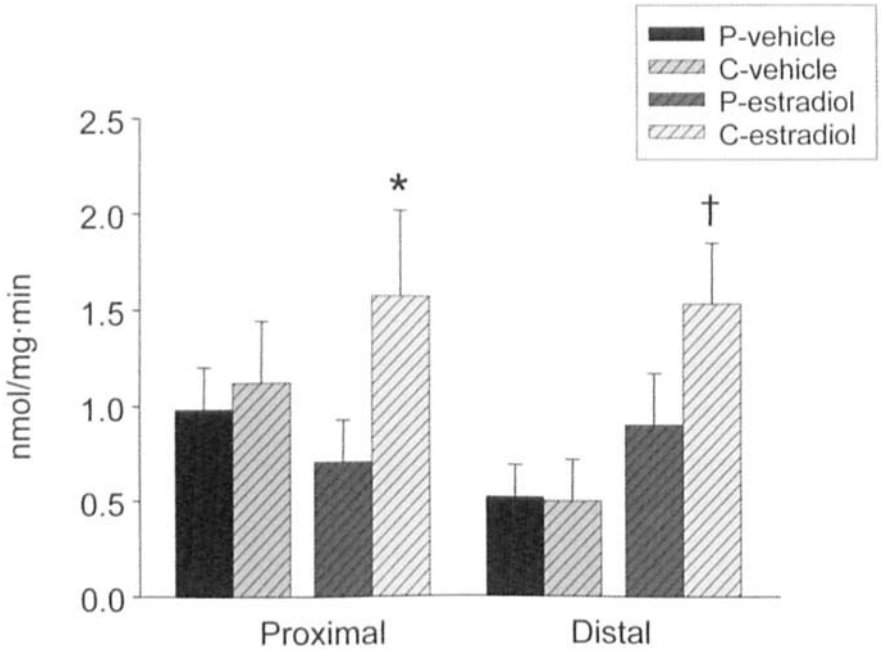

Figure 1. Rates of carrier-mediated glucose transport at 50 mmol/L by the proximal and distal small intestine of ovariectomized rats fed diets high in carbohydrate (C) or protein (P) and treated with either estradiol or vehicle. The asterisk indicates that a difference was detected for rats treated with estradiol and fed the two diets, and the cross is for a difference between rats treated with the vehicle and estradiol and fed the high-carbohydrate diet ($P < 0.05$).

with estradiol consumed 21% less food (Table 2). Rats fed the high-protein diet tended to eat more than those fed the high-carbohydrate diet (0.27 ± 0.02 g food/g body mass vs. 0.23 ± 0.02; $P = 0.07$).

Although averages for initial and final body mass did not differ among any of the groups (Table 2), the rats treated with vehicle maintained body mass, whereas administering estradiol resulted in a 7% decline in initial body mass ($P < 0.05$). The magnitude of decline in body mass caused by the estradiol treatment did not differ between diets.

Absolute intestinal length and mass did not vary among groups (Table 2). However, when intestinal dimensions were normalized to body mass, rats fed the high-protein diet (with and without estradiol treatment) had heavier small intestines (0.015 ± 0.001 g/g vs. 0.011 ± 0.001; $P < 0.05$) that were slightly longer (0.40 ± 0.02 cm/g vs. 0.37 ± 0.01; $P = 0.09$) than those of rats fed the high-carbohydrate diet. When fed the same diet, intestinal length and mass did not differ between rats treated with estradiol and those receiving vehicle despite the differences in food consumption and changes in body mass.

Serum Estradiol Concentrations. Serum concentrations of estradiol did not differ between rats fed the high-carbohydrate (C) and high-protein (P) diets and receiving the vehicle (1.84 ± 0.23 μg/L and 1.99 ± 0.22 μg/L, respectively) but were lower than those of rats fed the same diets and treated for 1 week with estradiol cypionate (3.08 ± 0.25 and 2.80 ± 0.32, respectively; $P < 0.05$).

Rates of Glucose Transport. Significant main effects were detected for treatment ($P = 0.06$), diet ($P = 0.06$), and the interaction between treatment and diet ($P = 0.10$) but not for region ($P = 0.25$) and any associated interactions ($P > 0.10$).

When rats were treated with vehicle, rates of glucose transport (nmol/mg·min) measured at 50 mmol/L did not differ between diet groups in either region (Fig. 1, first and third pairs of bars). The lack of differences between the two diet groups of vehicle-treated rats was also evident when rates of uptake transport in the proximal region were compared using all five concentrations of glucose (data not presented). Rates of glucose transport by the proximal region of both diet groups of vehicle-treated rats averaged more than 2-fold higher than those in the distal region, resulting in a declining proximal-to-distal gradient of glucose transport.

Administering estradiol for 7 days had two consequences. First, it resulted in higher rates of glucose transport. The increase was more pronounced in the distal region (Fig. 1), and this eliminated the declining proximal to distal gradient for both diet groups. Second, rats treated with estradiol were able to adaptively modulate glucose transport to match the differences in diet composition. Specifically, rates of transport by the estradiol-treated rats fed the C diet were higher than those of rats fed the P diet ($P < 0.05$). Although diet differences for the estradiol-treated rats did not reach significance in either region at 50 mmol/L ($P > 0.05$), paired comparison for all five concentrations measured in the proximal region averaged 64% higher for estradiol-treated rats fed the C diet ($P < 0.05$). A similar pattern of response to diet for estradiol-treated rats was observed for rates of glucose transport measured in the distal region at 0.0016 mmol/L (data not presented).

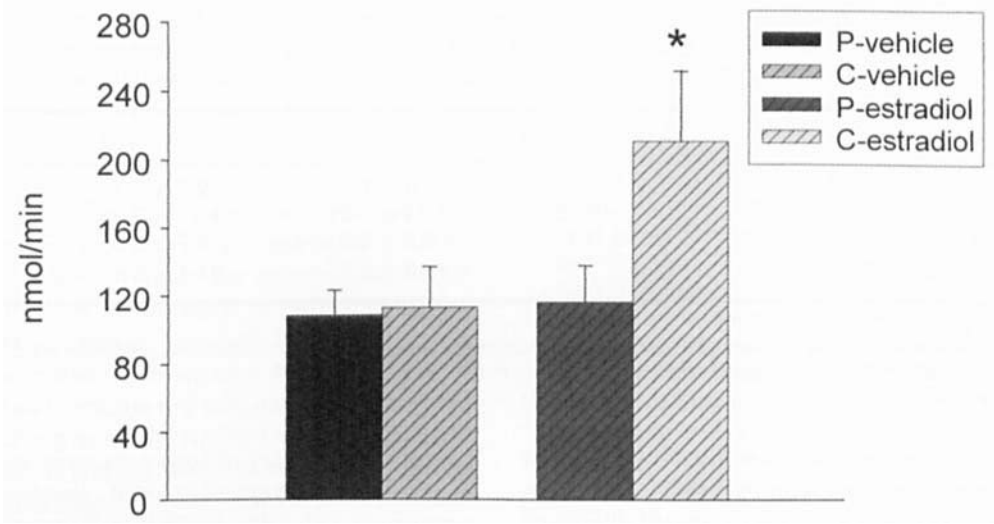

Figure 2. Capacities of the entire length of small intestine for carrier-mediated transport of glucose at 50 mmol/L when ovariectomized rats were fed diets high in either carbohydrate (C) or protein (P) and treated with either estradiol or vehicle. The asterisk indicates that a difference was detected between the rats treated with estradiol and fed the two diets ($P < 0.05$).

The lack of adaptive responses to the two diets for vehicle-treated rats was also evident from the similar glucose uptake capacities for rats fed the C and P diets (Fig. 2). In contrast, glucose transport capacities of estradiol-treated rats were nearly 2-fold higher when the rats were fed the C diet ($P = 0.03$).

Accumulation ratios for glucose uptake in the proximal and distal small intestine were significantly greater than a value of 1.0 (Table 3), verifying the presence of a saturable component of glucose absorption, but did not differ among treatments. Rats fed the C diet had higher V_{max} for glucose transport in the proximal small intestine after administration of estradiol, whereas V_{max} values for rats fed the high-protein diet did not differ between those receiving estradiol and vehicle (Table 3). The affinity constants (K_m) for glucose uptake did not differ among the four groups of rats.

Discussion

Administering estradiol to ovariectomized animals decreases food consumption and reduces weight gain (39, 40, present study). Therefore, the logical *a priori* expectation was that higher circulating concentrations of estradiol would result in a shorter, lighter small intestine with lower digestive capacities. Contrary to this expectation, administering estradiol to the ovariectomized rats did not result in small intestines with reduced abilities to transport glucose. These findings complement the increases in the activities of BBM disaccharidases, peptidases, and alkaline phosphatase (17) and absorption of calcium (20) when estradiol is administered to rats and the increased uptake of glucose and a synthetic growth hormone secretogogue when estradiol is administered to intact female dogs that are anestrus (35). Moreover, administering estradiol to ovariectomized rats increases amylolytic and tryptic activities in acinar cells isolated from the pancreas. However, the secretory responses of the exocrine pancreas to cholecytokinin are reduced by estradiol, and this has been related to lower densities of cholecystokinin receptors (41, 42).

The concentrations of estradiol measured in the rats receiving the vehicle were higher than the less than 1 μg/L reported in other studies of ovariectomized rats (43, 44). This may be related to our use of retired breeders that were ovariectomized at maturity and after producing several litters, whereas most other studies have used younger rats that were ovariectomized prior to having reproduced and may not have been sexually mature. It is likely the higher baseline concentrations of circulating estradiol in the larger, mature rats used in the present study were from extragonadal sources. The large mass of adipose tissue in adult rats is a likely source (39). Despite the greater contribution of extragonadal sources, the differences in circulating estradiol concentrations between vehicle- and estradiol-treated rats corresponded closely with those measured in other studies that used similar dosages (~20 μg estradiol/kg/day).

Although the estradiol administration resulted in circulating concentrations (3.1 and 2.8 μg/L in rats fed the C and P diets) that were lower than those reported for rats during proestrus (30–40 μg/L; Ref. 45), they were sufficiently high to reduce consumption of food and cause a loss of body mass when compared to rats treated with the vehicle. Yet the estradiol-treated rats did not have smaller intestines. Since the rats treated with the vehicle did not gain additional weight, the extragonadal sources may have provided sufficient estradiol to prevent the weight gain that is typical after ovariectomy. Alternatively, the 1-week period was not sufficiently long to detect an increase in body mass.

The higher rates of glucose transport measured in the rats treated with estradiol and fed diet C correspond with previous reports that estradiol treatment increases the uptake of glucose and a tripeptide derivative by the proximal small intestine of dogs (35), enterocyte calcium concentrations (46), and ion transport by the colon (47, 48) of rats.

Table 3. Accumulation Ratios and Kinetics Constants for Carrier-Mediated Transport of Glucose by the Proximal and Distal Small Intestine of Ovariectomized Rats Fed Diets High in Carbohydrate (C) or Protein (P) for 4 Weeks and Treated with Vehicle or Estradiol During the Last Week[a]

		C + vehicle	C + estradiol	P + vehicle	P + estradiol
Proximal	Accumulation ratio[b]	6.2 ± 1.1	5.8 ± 1.1	9.7 ± 2.7	14.7 ± 7.4
	V_{max}[c]	1.37 ± 0.32	1.83 ± 0.01	1.17 ± 0.20	0.90 ± 0.27
	K_m[d]	4.6 ± 0.4	6.2 ± 0.2	4.7 ± 0.3	3.5 ± 0.4
Distal	Accumulation ratio	13.0 ± 1.1	14.8 ± 2.7	24.1 ± 6.1	21.0 ± 7.1

[a] Values are means ± SEM.
[b] Calculated as the quotient for tissue accumulation of tracer in the absence and presence of 50 mmol /L unlabeled substrate.
[c] Maximum rates of carrier-mediated absorption (nmol/min·mg tissue mass).
[d] Affinity constant (mmol/L).

Moreover, the 2–3-fold higher rates and capacities of glucose transport are consistent with the 2–3-fold increases reported for intact (not ovariectomized) laboratory rodents fed diets with similar differences in nutrient composition (49). The reason why the ovariectomized rats treated with vehicle were unable to adaptively modulate glucose transport to match changes in diet composition is unexplained but may have clinical implications, particularly for postmenopausal women.

Even though the rats treated with estradiol ate less than those treated with the vehicle, rates and capacities for glucose transport actually increased (for diet C) or remained the same (for diet P). The disconnect between food consumption and rates of glucose transport after administration of estradiol indicates that at least some enterocyte characteristics are responsive to a combination of the concentrations and proportions of lumenal nutrients, the regulatory peptides associated with the GIT, and estradiol and other hormones from extra-GIT sources. It is possible that estradiol and perhaps other regulatory molecules play a role in influencing the adaptive responses.

Although the present study was not designed to address the question of how estradiol modulates absorption of nutrients, the present findings and our previous results for dogs (35) provide insights into some of the most plausible mechanisms. The higher rates of glucose transport by rats receiving estradiol and fed the C diet—and particularly in the distal intestine—suggests there was an increase in the total abundance of transporter protein. This could have been caused by the synthesis of new transporters (a genomic response). Alternatively, existing transporters could have been recruited from intracellular pools (a nongenomic response). The SGLT-1 densities are rapidly (<1 hr) and reversibly modulated in response to lumenal glucose concentrations (50, 51) or regulatory peptides (10–14, 52), with the densities of the peptide transporter, PEPT1, similarly modulated by lumenal nutrients (53, 54) and regulatory peptides (55–57).

Another possibility is that the combination of estradiol and the C diet caused a redistribution of enterocytes with transport functions along the crypt-villus axis, thereby increasing the total abundance of transporters and rates of transport. Exemplary of such a response are the lower rates of enterocyte proliferation and apoptosis during food deprivation (58, 59), leading to a greater proportion of enterocytes along the crypt-villus axis that are capable of transporting nutrients. Although various GIT regulatory peptides modulate enterocyte cytokinetics (60) and estradiol decreases proliferation of colonocytes (61), to our knowledge the influence of estradiol on rates of enterocyte proliferation and turnover is uncertain.

The estradiol-induced increase in glucose transport could also have been caused by the appearance of or a change in the relative abundances of alternative transporters. Although SGLT1 is considered to be the principal BBM transporter for glucose and other aldohexoses, there may be a heterogeneity of apical glucose transporters (62). The presence of the facilitated glucose transporter, GLUT2, in the BBM (63) would provide a lower-affinity, higher-capacity system. In fact, modulation of GLUT2 densities in the BBM may explain the rapid (<5 mins) decrease in phloridzin-insensitive glucose uptake after enterocytes are exposed to leptin (64). However, administering estradiol did not change the apparent affinity constant, making it unlikely that the increased uptake of glucose was caused by the appearance of or a change in the relative abundance of alternative transporters.

Another explanation for the increased transport of glucose would be a higher activity of existing transporters. This could result with a decrease in BBM viscosity (65–69). The higher Na-K-ATPase and alkaline phosphatase activities of ileal enterocytes after administering estradiol (70, 71) or prolactin (72), respectively, are associated with higher BBM fluidity. In addition to a potentially faster transporter turnover, the higher Na-K-ATPase activity could enhance transport of nutrients coupled to ion gradients, including glucose and peptides. However, the present results do not support a change in fluidity as the principal mechanism for the increased uptake. If estradiol influences distal small intestine BBM fluidity, increases ion gradients, or enhances transporter functions, rates of glucose transport would have increased in parallel for rats fed the C and P groups.

In addition to increasing rates of carrier-mediated uptake, estradiol could enhance carrier-independent pathways of

absorption (e.g., paracellular uptake and diffusion through the BBM). If there had been an increase in absorption *via* the paracellular or BBM diffusion pathways, tissue accumulation of the labeled L-glucose would have differed between estradiol and vehicle groups. Such differences were not detected at any concentration of D-glucose.

Even though gender differences for digestion and pharmacokinetics are recognized and manifold (31–34), surprisingly little is known about the influence of normal or induced fluctuations of estradiol on BBM functions, including nutrient absorption. Although the present results demonstrate that estradiol influences the absorption of nutrients by the small intestines of rats, there are differences from what we have previously reported for dogs. Specifically, the increase in glucose transport after administering estradiol to anestrus dogs (35) was of a greater magnitude compared to the present results for rats. Our findings for rats and dogs indicate the responses to estradiol vary among species, can be influenced by diet composition, and may not be consistent among different transporters (35).

Finally, are the responses of the transporters to administration of estradiol of clinical significance? In our previous study with dogs, the higher rates of absorption for a tripeptide derivative (a growth hormone secretogogue) after administering estradiol to intact dogs corresponded with peak systemic availability that was increased by three orders of magnitude and occurred much earlier (35). These findings indicate that the modulation of nutrient uptake by estradiol can influence the systemic availability of nutrients as well as drugs that are targeted to responsive transporters. There is a need to elucidate the mechanisms that are responsible for the influence of estradiol on rates and adaptive modulation of nutrient transport.

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