Magnitude of functional adaptation after intestinal resection

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O’Connor, Timothy P., Mandy M. Lam, and Jared Diamond. Magnitude of functional adaptation after intestinal resection. Am. J. Physiol. 276 (Regulatory Integrative Comp. Physiol. 45): R1265–R1275, 1999.—Intestinal adaptation after resection has been much studied, but rarely examined in an integrative context. Hence we assessed the effects of resection and subsequent adaptation on the quantitative relationship between dietary glucose load and gut capacity to transport glucose. The ratio of capacity to load is termed the “safety factor.” Our objectives were to determine 1) the time course of intestinal adaptation after resection, 2) whether adaptation is quantitatively complete, 3) whether survival requires maintaining a safety factor of at least 1.0 for glucose transport, 4) the effect of altered energy demands on adaptation, and 5) the relationship between the amount of tissue removed and the magnitude of functional adaptation. We performed 80% resection of the small intestine on Sprague-Dawley rats and measured small intestinal glucose uptake capacity, dietary glucose load, and gut gross morphology at 1, 5, and 10 wk postsurgery. Nearly all aspects of adaptation were complete by 1 wk postsurgery. After resection, remnant small intestine mass increased by over fivefold within 1 wk, to reach 50–70% of its preresection value. However, mass-specific glucose uptake activity was reduced, so that intestinal regeneration restored uptake capacity to only 33% of control values. Increased energetic demands had only modest effects on intestinal adaptation. Although the safety factor for small intestinal glucose uptake remained <1.0 (i.e., capacity < load) after adaptation to resection, nearly all rats survived. Hindgut fermentation of nonabsorbed nutrients appeared to contribute to that survival, despite inadequate small intestinal capacity. After less massive resection surgeries (25, 50, and 75% resections), the percent increase in glucose uptake capacity increased with the amount of tissue removed.

Adaptation after gut resection is a model of adaptive plasticity in intestinal function that is also clinically important. This study demonstrates that small intestinal adaptation after resection is not complete within the very short postoperative time courses examined in this study. The inability to maintain 100% functional adaptation after resection may be important in understanding the clinical outcomes of intestinal surgery. Understanding the relationship between dietary glucose load and gut capacity to transport glucose is essential for understanding the regulation of intestinal function.

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resection and that resections that reduced intestinal safety factors <1.0 (i.e., load greater than capacity) would be fatal, as was the case in their study. A related hypothesis is that survival of resection depends on the ability quickly to regenerate intestinal capacity (perhaps by mobilizing stored energy reserves) and thus recover to an intestinal safety factor of at least 1.0. This study will address both of these related hypotheses.

The energetic costs of normal body maintenance, as well as the cost of intestinal regeneration after resection, must be derived from the assimilation of energy coming from ingested food plus energy derived from the mobilization of stored reserves. Thus if the cost of normal body maintenance could be reduced, then the ability to survive massive resection and/or the time course to recovery from resection could be improved. Conversely, increased maintenance costs could reduce survivorship and/or prolong the time course of intestinal adaptation. Exposure to cold ambient temperature increases the maintenance costs of rats and may therefore affect intestinal adaptation after resection. Hence our study also examines the effect of total energy demand on intestinal adaptation.

We assessed the effects of resection and subsequent adaptation on the quantitative relationship between dietary glucose load and the gut’s capacity to transport glucose. Specifically, we shall address the following questions about intestinal resection in rats. 1) What is the time course for functional adaptation after resection surgery? 2) Is functional adaptation quantitatively complete after massive small intestinal resection (i.e., does adaptation restore uptake capacity to 100% of its presection value)? 3) Is survival dependent on maintaining (or restoring) intestinal capacity at least equal to dietary load? 4) What is the effect of altered energetic demand on intestinal adaptation? 5) What is the relationship between the amount of tissue removed and the magnitude of functional adaptation?

METHODS

Animals and experimental design. Female Sprague-Dawley rats from Charles River Laboratories (Wilmington, MA) were maintained in the University of California Los Angeles Health Sciences Vivarium at 23°C on a 12:12-h light-dark cycle with ad libitum access to water and a sucrose-based diet [ICN Biochemical, Cleveland, OH, see Diamond and Karasov (8) for diet composition] for at least 14 days before surgery. The carbohydrate content of the diet was 55% sucrose and 15% fiber.

We used 48 rats to address questions 1-4 posed in the introduction. Rats were initially divided into three surgical treatment groups (surgery methods described below): control (no surgery), 0% resection of small intestine (i.e., transection and reanastomosis), and 80% resection of small intestine. Within each of those three groups, rats were divided into two subgroups on the basis of maintenance temperature after surgery: 23 and 5°C. Individuals from each subgroup were killed at one of three times postsurgery: 1, 5, and 10 wk. The initial sample sizes within each of the six combinations of temperature treatment and postsurgery time (2 temperatures × 3 recovery times) were three control rats, one 0%-resected rat, and four 80%-resected rats.

We used an additional 16 rats to address the fifth question posed in the introduction, that of the relationship between the amount of tissue removed and the magnitude of functional adaptation. These rats were divided into four surgical treatment groups of four rats each: 0, 25, 50, and 75% resection. All of these rats were maintained at 23°C and killed 4 wk after surgery.

Surgeries. Rats were denied access to solid food, but allowed free access to water, for 24 h before surgery. Individuals were weighed and anesthetized with Nembutal (0.1 ml/100 g ip). Abdominal hair was clipped, and the abdomen was aseptically prepared for surgery. The small intestine was exteriorized through a ventral median laparotomy and its length measured from the ligament of Treitz to the ileocecal junction using a piece of sterile surgical thread. After determining the specific length of intestine to be removed and its position (centered in the middle of the measured length), we ligated and cut blood vessels supplying that segment and then out and removed the segment. The proximal and distal ends of the remnant intestine were reanastomosed with 6–0 silk suture in a simple interrupted pattern. The abdomen was closed with two layers of 3–0 polyglycolic acid suture, each with a running stitch pattern. Rats were allowed access to solid food 24 h after surgery. Transection (0% resection) treatment consisted of an identical surgery procedure, including cutting and reanastomosing the intestine, but no intestine was removed. Control rats did not undergo any surgery.

To examine the effect of total energy demand on intestinal adaptation, rats were divided into two energy demand groups after surgery. About 24 h after surgery, one group (along with their corresponding controls) was placed at 5°C, whereas the other treatment group (and their controls) remained at room temperature (23°C).

Food intake and glucose load. Food intake, glucose load, and digestive efficiency were measured each day for 3 days before death, as previously described (11). Briefly, rats were maintained in cages with wire bottoms that allowed feces and ords to drop to a tray below. Feces and ords were collected, separated, and weighed each day. Daily food intake was calculated as the mass of food disappearing from the food dispenser each day minus the mass of the collected ords. Glucose load (in units of mmol/day) was taken as the mass of food eaten times the sucrose content of the food (because 1 mol of sucrose on hydrolysis yields 1 mol of glucose). We calculated apparent dry-matter digestibility as food intake minus fecal output divided by food intake.

Glucose uptake assay and safety factors. The activity of the Na+-glucose cotransporter (SGLT-1) was measured by the everted sleeve method described in detail previously (8, 16). To minimize any circadian effects, all intestinal capacity measurements were conducted between 8 AM and 1 PM. Briefly, rats were anesthetized with an intraperitoneal injection of 0.2–0.25 ml Nembutal, a laparotomy was performed, and the entire small intestine from pylorus to ileocecal junction was perfused with ice-cold Ringer solution and then dissected out. For control and transection rats, the small intestine was divided into equal-length thirds (termed the proximal, middle, and distal regions). For resected rats, the middle region had been removed during resection surgery, so their intestine was divided into only two regions: proximal to and distal to the anastomosis. For all animals, each intestinal region was lightly blotted dry and weighed. The wet mass of the small intestine was taken as the sum of these two or three regional wet masses. Each of the intestinal regions was then everted over a stainless steel rod. From the middle of each region we cut at least two sleeves for use in glucose uptake assays. Uptake activity was normalized to milligram wet.
mass of the tissue. Uptake capacity was calculated for each region of the small intestine as the product of mass-specific activity times regional wet mass. Total intestinal uptake capacity was taken as the sum of regional capacities.

The relationship between a physiological capacity and the load on it can be described by the ratio of capacity to load, also known as the safety factor (3). The safety factor for glucose uptake is thus the ratio of uptake capacity to dietary glucose load. Of course, as is the case for all in vitro assays, there may be differences between our in vitro measure of glucose uptake activity and the in vivo activities. Such differences could result in errors in estimating an animal’s safety factor, but the everted sleeve method minimizes such errors (see Ref. 21 for discussion).

Intestinal morphology and organ masses. Wet and dry mass values for the stomach, small intestine, cecum, large intestine, and vital organs (heart, lungs, liver, spleen, and paired kidneys) were measured as described previously (12). The organs were removed and weighed wet after all fat was trimmed off and then weighed again after being dried for at least 48 h at 60°C.

Statistics. Our experimental design for addressing the first four questions posed in the introduction consisted of three independent variables: 1) surgery, which comprised three levels (control, 0% resected, and 80% resected), 2) time postsurgery, which comprised three levels (1, 5, and 10 wk), and 3) postsurgery maintenance temperature, which comprised two levels (23 and 5°C). Hence we initially used a 3 × 3 × 2 ANOVA to assess effects of these independent variables on many dependent variables, including body mass, food intake and digestibility, glucose uptake activity and capacity, and morphological measurements. In general, any morphological or functional effects of transection (0% resection) surgery are slight and transient (4), and on the basis of previous studies (13, 23, 26) we did not expect significant differences between control rats (no surgery) and sham operated (0% resection) rats. In fact, we did not detect a significant difference between control rats and 0%-resected rats for any of the dependent variables that we measured (using a Tukey test for pairwise comparisons), so we pooled their values and reanalyzed the data using a 2 × 3 design. Given that there was only a single 0%-resected rat for each time and temperature treatment, the pooling had little qualitative effect on our results, but it did slightly increase our statistical power in an effort to reduce type II statistical errors that are possible with our sample sizes (see RESULTS). Because some of our dependent variables are known to covary with body mass (e.g., food intake, intestine mass, glucose uptake capacity, and organ masses), we tested body mass as a covariate and performed analysis of covariance (ANCOVA) on these variables when it proved significant.

The experimental design for addressing the fifth question posed in the introduction consisted of a single independent variable, surgical treatment, which comprised four levels (0%, 25%, 50%, and 75% resections). We used ANOVA and ANCOVA to assess the effects of the amount of tissue removed on the dependent variables described above.

The text and figures give mean values ± SE. All analyses were performed using Systat 7.0 (Chicago, IL), and the level P < 0.05 was regarded as statistically significant throughout.

RESULTS

All of the following results apply to the 80%-resected rats, except for the final paragraph of RESULTS, which describes results of resections of < 80%.

Survival, body mass, and food intake. Out of the initial group of 48 rats, four died after surgery. All four were being maintained in the cold: one rat in the week 1 resected group and three rats in the week 10 resected group. Three of the four deaths occurred within 1 wk after surgery, and all three of these deaths appeared to result from surgical complications such as a leak in the intestinal anastomosis or occlusion of the intestinal vasculature. The fourth death occurred 5 wk after surgery, and the cause of death was unknown. Thus each of our 12 experimental groups (2 surgery × 3 times postsurgery × 2 temperatures) had a sample size of four rats, except for the week 1 and week 10 resected groups in the cold, which had 3 rats and 1 rat, respectively. Hence the final sample size for the entire experiment was 44 rats.

Resection surgery had a significant effect (P < 0.001) on body mass, with resected rats weighing less than controls (Fig. 1). The reduction in body mass of resected animals compared with controls was much greater than the −5 g mass of intestine that was removed. However, both resected and control rats showed significant increase in body mass over time (P < 0.001). The fact that the surgery × time interaction effect was not significant (P > 0.27) implies that the rate of mass increase was not significantly different between the two groups. Temperature had a modest but significant (P < 0.05) effect on body mass, which was reduced at the lower temperature (Fig. 1).

Fig. 1. Effect of resection on body mass in rats maintained at 23 A) and 5°C B). Note that resected rats continued to increase in mass over time, even when maintained in cold. ○, data from control animals; ■, 80%-resected animals; error bars represent ± SE. In some cases, error bars are not visible because they are smaller than symbol for mean value, and in other cases, symbols for control and resected rats are slightly displaced from each other for clarity (e.g., symbols for body mass in rats maintained at 5°C).
Neither resection (P > 0.2) nor time (P > 0.05) had a significant effect on food intake (Fig. 2). However, rats maintained in the cold ate ~60% more food per day than those maintained at room temperature (P < 0.001; Fig. 2). There was no significant effect of surgery (P > 0.1), time (P > 0.2), or temperature (P > 0.4) on apparent dry-matter digestibility (grand mean 81.7 ± 0.3% for all animals).

Intestinal morphology and vital organ masses. By comparing the mass of the resected intestine to known intestinal masses of similar-sized rats, we estimated that our resection surgery attempting to remove 80% of small intestinal length removed ~90% of the small intestine mass. Within 1 wk after surgery, the mass of the remnant small intestine increased greatly in resected rats, back up to 55% of its original (presurgery) mass in individuals maintained at room temperature (Fig. 3). However, there was no significant effect of time between 1 and 10 wk postsurgery on intestinal mass (P > 0.05), and hence control rats continued to have a greater intestinal mass than resected rats (P < 0.001; Fig. 3, A and B). In other words, although the resected rats quickly increased the mass of their remnant small intestine by over fivefold, there was no observed further increase after 1 wk, and regeneration did not restore the intestinal mass to its presurgery value. Rats maintained in the cold had significantly greater intestinal mass than those maintained at room temperature (P < 0.001; Fig. 3, A and B). The same patterns were found when intestinal dry masses were analyzed.

We also estimated the length of the remnant small intestine after surgery and calculated that our protocol removed ~80% of intestinal length. Remarkably, there was no effect of either time (P > 0.15) or temperature (P > 0.5) on intestinal length (Fig. 3, C and D). Naturally, resected animals had a much shorter small intestine than controls (P < 0.001; Fig. 3, C and D). That is, intestinal length did not recover at all. Body mass was not a significant covariate for food intake or small intestinal mass or length, so all of the P values above are from an ANOVA (as opposed to an ANCOVA).
There was no significant effect of time postsurgery on either cecum or large intestine mass (P > 0.18 and P > 0.35, respectively), hence values from each time are pooled together. Mass of both of these hindgut components was significantly greater in resected rats and in individuals maintained in cold, suggesting increased fermentation activity under these circumstances. Values shown for large intestine represent adjusted mean values from an analysis of covariance, because body mass proved to be a significant (P < 0.05) covariate (i.e., values shown already account for differences in body mass). Body mass was not a significant covariate for cecum mass (P > 0.45), so cecum mass values were not adjusted.

Body mass proved to be a significant covariate in ANCOVAs of wet and dry masses of liver, heart, lungs, and kidney, but not spleen. Resection surgery did not have a significant effect on the wet mass of the liver (P > 0.13), heart (P > 0.17), lungs (P > 0.36), or spleen (P > 0.6). Although kidney wet mass was slightly (6%) but significantly (P < 0.04), greater in resected rats than controls, the effect was not significant for kidney dry mass (P > 0.25). None of the organs other than the kidneys showed any corresponding differences between wet and dry mass analyses. All of the organs, except the spleen, showed a similar response to temperature and time (Fig. 5). Specifically, there was a significant (or nearly significant, in the case of heart mass) temperature × time interaction effect on the wet and dry mass of kidneys (A), liver (B), heart (C), and lungs (D). There was no effect of resection surgery on wet mass of any organ, so values from resected and control animals were pooled for this figure. Body mass was a significant covariate for each organ mass, so all values represent adjusted means. Note that organ masses tend to increase with time in rats maintained at 5°C compared with rats maintained at 23°C.
masses (the following P values are for wet masses) of the liver (P < 0.01), heart (P < 0.06), lungs (P < 0.04), and kidneys (P < 0.01). In each case, the organ masses (adjusted for body mass) tended to increase over time in animals that were maintained at 5°C and to decrease over time in animals maintained at 23°C (Fig. 5).

Glucose uptake activity, capacity, and safety factors. The activity of the Na\(^+\)-glucose cotransporter can be expressed in units of glucose uptake per milligram or per centimeter of intestine. When expressed on a per milligram basis, there was not a significant effect of either time (P > 0.8) or temperature (P > 0.08) on glucose uptake activity in the proximal region, but values for resected rats were only ~60% of control values (P < 0.001; Fig. 6). There was a significant surgery × temperature interaction effect (P < 0.03) on distal uptake activity (per mg), but no significant effect of time (P > 0.4; Fig. 6, C and D).

When expressed on a per centimeter basis, neither resection (P > 0.8) nor time (P > 0.14) had a significant effect on glucose uptake activity in the proximal region of the small intestine (Fig. 7, A and B), and the effect of temperature was modest, although statistically significant (P < 0.05). In the distal small intestine, in
contrast, uptake activity (per cm) was significantly greater in resected rats than in controls (P < 0.001; Fig. 7, C and D), but there was not a significant effect of temperature (P > 0.15) or time (P > 0.2). Note that, regardless of the units used to express uptake activity, there was not a single case in which time proved to be a significant factor.

The differences in glucose uptake activity expressed per milligram compared with those expressed per centimeter reflect the increased mass per unit length (mg/cm) of the small intestine of resected rats. That is, after resection, the mass of the remnant intestine increased by over fivefold without any increase in length (Fig. 3). Hence the mass per unit length of intestine in resected rats was much greater than that in control rats. Because the uptake per milligram decreased with resection (Fig. 6) but milligram per centimeter increased (Fig. 3), their product of uptake per centimeter (Fig. 7) remained unchanged (proximally) or increased (distally).

We also measured glucose uptake activity in the cecum and large intestine, but found activities and capacities that were <1% of those of the small intestine. Hence the contribution of the hindgut directly to glucose transport is negligible (but see below for the role of the hindgut in dealing with nutrients that are not absorbed in the small intestine).

Passive glucose uptake could in principle provide additional uptake capacity, but previous measurements showed passive glucose uptake to be <6% of total glucose uptake in unanesthetized rats in vivo (25). In the current study, we used l-glucose space (in µl/mg) as an indicator of passive uptake of glucose and found no significant variation due to either resection (P > 0.12) or temperature (P > 0.2).

Body mass was not a significant covariate for glucose uptake capacity or safety factors, so both were analyzed using ANOVA. Glucose uptake capacity of the entire small intestine did not vary significantly over time (P > 0.08), and resected rats’ uptake capacity was only 30 and 38% of control values at 23 and 5°C, respectively (Fig. 8; P < 0.001). The lower glucose uptake capacity of resected rats is the result of the fact that their intestinal mass (Fig. 3, A and B) and their mass-specific uptake activities (Fig. 6) were both less than those of controls. Glucose uptake capacity was slightly, but significantly (P < 0.04), greater in rats maintained at 5°C than in those maintained at 23°C (Fig. 8).

The safety factor for the glucose transporter is defined as uptake capacity divided by dietary glucose load. Because resected rats had a lower uptake capacity than control rats (Fig. 8), without any significant changes in dietary load (Fig. 2), their safety factors were significantly lower than those of control rats (P <
0.001; Fig. 9). There was no significant effect of time on the safety factor for the glucose transporter ($P > 0.05$), but the safety factors of rats maintained in the cold were significantly lower than for those maintained at room temperature ($P < 0.001$; Fig. 9). Safety factors of resected rats ranged from 0.18 to 0.35, indicating that they were consuming about three to five times more glucose than they were capable of transporting across the brush border of their small intestine. Control rats at 23°C maintained safety factors that did not differ significantly from 1.0 (mean value of 1.01 ± 0.04, $P > 0.8$ by t-test), whereas the safety factors for rats kept at 5°C were significantly <1.0 (mean value of 0.76 ± 0.03, $P < 0.001$ by t-test).

Effect of amount of tissue removed. To assess the relationship between the amount of tissue removed and the magnitude of functional adaptation, we performed 0 (transection), 25, 50, and 75% resection surgeries on a separate group of rats. We measured the extent of adaptation 4 wk after surgery, a period sufficient for complete adaptation as demonstrated by the results above. The amount of intestine resected did not have a significant effect on body mass ($P > 0.28$), food intake ($P > 0.6$), digestibility ($P > 0.41$), cecum mass ($P > 0.37$ and $P > 0.21$ for wet and dry masses, respectively), large intestine mass ($P > 0.15$ and $P > 0.31$ for wet and dry masses, respectively), or glucose uptake activity per milligram ($P > 0.12$ and $P > 0.36$ for proximal and distal regions, respectively) or per centimeter ($P > 0.20$ and $P > 0.46$ for proximal and distal regions, respectively). Intestinal mass ($P < 0.01$) and glucose uptake capacity ($P < 0.01$) decreased significantly with increased amounts of tissue removed (Fig. 10, A and B). Although adaptation was not quantitatively complete (i.e., capacities were not completely restored to presurgery values) at any level of resection, both the absolute and relative magnitudes of functional adaptation increased significantly ($P < 0.001$) with the percent resection (Fig. 10C). That is, the absolute increase and the percent increase in intestinal mass and glucose uptake capacity after resection were both greatest in rats that had the most tissue removed.

DISCUSSION

Our discussion refers to results from the 48 rats used in the massive (80%) resection portion of the experimental design, except where we specifically refer to results from other levels of resection surgery.

Time course and magnitude of adaptation. The first question that we posed in the introduction concerned the time course of intestinal adaptation after resection. The morphological and functional adaptations that we observed were both complete within 1 wk; there were no further changes in the variables that we measured between 1 and 10 wk postsurgery. Hence we shall now discuss these first-week changes.

Within 1 wk after resection surgery, the mass of the remnant intestine increased over fivefold without any change in length (Fig. 3). Previous studies (4, 27, 32) documented that morphological adaptation after resection is due to hyperplasia. Specific morphological changes include increased crypt depth and increased villus length and width. The rate of cellular proliferation in the crypts increases, as does the migration rate of enterocytes along the lengthened villi. Cumulatively, these changes result in increased intestinal circumfer-
ence and hence increased mass per unit length. Our results corroborate previous studies, which also suggest that most morphological adaptation takes place within 1–2 wk after resection surgery (15, 22).

We found that the mass-specific rates of glucose uptake were generally reduced in resected rats compared with controls (Fig. 6). Hence the magnitude of the functional adaptation (in glucose uptake) that occurred within 1 wk was less than the magnitude of the observed morphological adaptation, particularly in the proximal region of the intestine. This difference is generally attributed to a decreased proportion of functionally mature enterocytes on the lengthened villus (see e.g., Refs. 9, 19, 31). The proportion of mature enterocytes per villus is a consequence of many variables, including crypt cell production rate, cell migration rate, villus length, and enterocyte time to maturity. Our glucose uptake results for the proximal intestine at both temperatures (Fig. 6, A and B) and for the distal region in the cold (Fig. 6D) are consistent with the possibility of a reduced proportion of mature enterocytes per villus. Our results also suggest that the distal villi of rats housed at room temperature maintained a relatively constant proportion of mature enterocytes after resection (Fig. 6C).

Freeman et al. (10) found that mass-specific glucose uptake activity in the distal intestine of resected animals was significantly greater than in control animals at 6 wk, but not 2 wk, after resection surgery. In contrast, we found no difference between resected animals and controls in mass-specific transport rates in the distal intestine at any time after resection (Fig. 7C).

One explanation for these contradictory results is the differing techniques used for measuring transport rates. Freeman et al. (10) prepared membrane vesicles from mucosal scrapings pooled from multiple animals and then performed a rapid (5 s) filtration technique for assessing glucose transport. They detected two systems for glucose transport with differing kinetics, but they did not find any measurable sodium-dependent glucose transport in the ileum of control rats (at any time) or resected rats at 2 wk postsurgery. The only detectable transport in the distal intestine was found in resected rats and then only 6 wk after surgery (hence the lack of a difference between control and resected rats at 2 wk after surgery was due to the fact that no activity was found in either group at that time). Whang et al. (31) recognized the difficulties of directly comparing results from studies of intact tissues with those using reductionist methodologies, and they examined glucose transport normalized to mucosal surface area. They found that at 2 wk after resection surgery, intestinal adaptation depended primarily on increased absorptive surface area, rather than on enhanced functional capacity of individual enterocytes. Extending a study such as theirs to a longer time course could help resolve remaining differences between studies that use different techniques.

The most relevant measure of adaptation on an organ/segmental basis is the functional capacity of the entire intestine. On this basis, the answer to the second question that we posed in the introduction is that adaptive hyperplasia clearly does not restore glucose uptake capacity to its preresection value (Fig. 8). Although functional adaptation is less than complete, the hyperplasia that occurs after massive (80%) resection is significant in that glucose uptake capacity does increase three- to fourfold within 1 wk (compared with the estimated uptake capacity of the remnant intestine immediately after surgery; see Fig. 8). However, there is no further functional adaptation after week 1, and the uptake capacity of resected individuals is restored only to about one-third of its original (preresection) value.

In fact, we found that quantitative adaptation in rats was not complete even at lower levels of resection surgery (Fig. 10). In contrast, Hammond et al. (13) found complete restoration of intestinal mass and glucose uptake capacity in mice after 25 and 50% resection surgery. We attribute this contrast to species differences, and we discuss associated aspects of this distinction below. Although functional adaptation is not complete at any level of resection in rats, the absolute and magnitude of adaptation does increase with the percent of intestine removed (Fig. 10C). Our results corroborate previous morphological findings (14), extend them to include functional measures, and thus address the fifth question posed in the introduction.

Survival after intestinal resection. The third question that we posed in the introduction addressed the hypothesis of Hammond et al. (13) that survival after resection surgery was dependent on maintaining a safety factor (i.e., capacity-to-load ratio) of at least 1.0. We suggested an alternative hypothesis: that survival after resection surgery was dependent on the ability to recover to an intestinal safety factor of at least 1.0 (perhaps through rebuilding intestinal capacity by mobilizing stored energy reserves). On the basis of our results (Fig. 9), we can clearly reject both of these hypotheses as applied to rats. Initially, one of our most surprising findings was that control rats only possess an intestinal safety factor of ~1.0 for glucose uptake (Fig. 9A). Intestinal safety factors for the glucose transporter and for sucrase in mice are normally 3–4 and only decrease to 1–2 when increased energetic demands such as lactation and cold temperatures result in dramatically increased nutrient loads (12, 13). Rats’ safety factor of ~1.0 under non-demanding conditions would seem to imply that brush border carrier-mediated glucose uptake capacity is close to rate limiting, with almost no small intestinal reserve capacity available for absorbing additional glucose.

We propose that the explanation for this initially surprising result (21) might also explain how rats survive massive resections even with intestinal absorptive capacities that are only ~20–40% of dietary load (Fig. 9). Briefly, rats are accomplished hindgut fermenters that can recover energy from nutrients not absorbed in the small intestine (28). Such nutrients are fermented into short-chain fatty acids by the bacterial flora of the cecum and large intestine and are then absorbed and used as an energy source. This process thereby serves as a built-in “reserve capacity” over and
above the glucose uptake capacity of the small intestine itself. Similar to rabbits (5), rats ferment not only dietary fiber but also any simple carbohydrates reaching the cecum (6). In fact, Kim et al. (18) found that 30–40% of ingested lactose (in rats fed a lactose diet) escaped the small intestine and was fermented in the hindgut. Thus even in normal rats, a substantial proportion of ingested simple sugars is likely to spill into the hindgut. Our measurements show that, although the uptake capacity of the small intestine itself provides rats with no reserve capacity for glucose transport, the hindgut provides considerable reserve capacity.

The reserve capacity function of the hindgut takes on an even more critical role in resected rats with severely compromised absorptive capacities (Fig. 8). The doubling of cecum mass that we observed at 5°C (Fig. 4A) suggests that hindgut fermentation plays an increased role in energy balance after resection. This interpretation receives independent support from measurements of hydrogen production. (H₂ gas is a by-product of fermentation, so increased levels of breath H₂ indicate increased fermentation activity.) Resected rats maintained in the cold showed a three- to fourfold increase in H₂ production compared with controls; that difference suggests increased reliance on fermentation after resection (J. Ty, M. M. Lam, and T. P. O’Connor, unpublished observations). Previous studies corroborate this conclusion and provide further evidence (such as increased short-chain fatty acid production) that increased hindgut fermentation is important as an adaptation to intestinal resection (e.g., Refs. 1, 2, 17). By revealing the large discrepancy between dietary load and the absorptive capacity of the small intestine, even after small intestinal hyperplasia (Fig. 9), ours is the first study to suggest the magnitude of the contribution of hindgut fermentation to overall energy balance.

Recall that different species are able to survive different magnitudes of intestinal resection. The hypothesis of Hammond et al. (13) regarding survivability of resections remains viable, but it may apply only to species with low hindgut fermentation capacities. For those species whose fermentation capacities are greater, such as rats and rabbits, the hypothesis would need to be revised to include not only small intestinal absorptive capacity, but also fermentation capacity. Whether or not species differences in fermentation capacity explain the observed ability of rats to survive much more extensive small intestinal resection than mice remains an open (but testable) question. Mathematical models of digestion suggest that rats would have a greater capacity for fermentation than mice due to their larger body size and longer transit times (see Ref. 7 for review of models). Morphological evidence supports this prediction in that the hindgut represents a substantially greater fraction of total intestinal mass (consisting of small intestine, cecum, and large intestine) in rats than it does in mice. The hindgut mass is 29% of the total intestinal mass in rats, but only 5% in mice (rat data are from this study, mouse data are from Ref. 12).

Effect of altered energy demand on functional adaptation. The fourth question that we posed in the introduction concerned the possibility that altering the body's energetic maintenance costs could affect the time course and/or the extent of intestinal regeneration. Maintaining rats at 5°C after resection surgery increased their maintenance costs, as reflected in the 60% increase in daily food intake (Fig. 2) and the increased masses of the kidneys, liver, heart, and lungs (Fig. 5) compared with rats maintained at room temperature. However, there were only modest effects of increased maintenance costs on small intestinal regeneration. The glucose uptake capacity of control rats maintained in the cold was only modestly greater than in those at room temperature (Fig. 8). After resection, intestinal regeneration restored uptake capacities to ~30% of their preresection values, regardless of maintenance temperature; the lack of a significant interaction effect involving temperature underscores the absence of an effect on the extent or time course of intestinal regeneration (Fig. 8). Because intestinal capacities did not increase as much as dietary loads, individuals maintained in the cold had lower safety factors than those maintained at room temperature (Fig. 9). Thus the safety factor even in nonresected rats was reduced below 1.0 when they were maintained in the cold.

Instead, the extra adaptation of resected rats at 5°C appears to be in the hindgut, not in the small intestine. Presumably, the increased hindgut mass of these individuals (Fig. 4) reflects increased fermentation activity contributing to their energy balance. The importance of fermentation capacity is also illustrated by resected rats that were maintained in the cold. They had the lowest safety factors (ranging from 0.2 to 0.3), but also had a cecum that was twice as big as that of control rats.

Perspectives

We conclude by briefly mentioning two directions for future research.

First, a complement to our study would be a quantitative assessment of nutrient fermentation. One could thereby partition total sugar digestion into the contributions of 1) small intestinal hydrolysis and uptake and 2) cecal and large intestinal fermentation.

Second, another complement to our study would be to examine adaptation of intestinal capacities besides glucose transport, such as hydrolytic capacities and transporters of other solutes.

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