Effects of meal size on postprandial responses in juvenile Burmese pythons (*Python molurus*)

STEPHEN M. SECOR AND JARED DIAMOND
Department of Physiology, University of California, Los Angeles, School of Medicine, Los Angeles, California 90095–1751

Secor, Stephen M., and Jared Diamond. Effects of meal size on postprandial responses in juvenile Burmese pythons (*Python molurus*). *Am. J. Physiol.* 272 (*Regulatory Integrative Comp. Physiol.* 41): R902–R912, 1997.—Pythons were reported previously to exhibit large changes in intestinal mass and transporter activities on consuming meals equal to 25% of the snake's body mass. This paper examines how those and other adaptive responses to feeding vary with meal size (5, 25, or 65% of body mass). Larger meals took longer to pass through the stomach and small intestine. After ingestion of a meal, O_2 consumption rates rose to up to 32 times fasting levels and remained significantly elevated for up to 13 days. This specific dynamic action equaled 29–36% of ingested energy. After 25 and 65% size meals, plasma Cl^- significantly dropped, whereas plasma CO_2, glucose, creatinine, and urea nitrogen increased as much as a factor of 2.3–4.2. Within 1 day the intestinal mucosal mass more than doubled, and masses of the intestinal serosa, liver, stomach, pancreas, and kidneys also increased. Intestinal uptake rates of amino acids and of D-glucose increased by up to 43 times fasting levels, whereas uptake capacities increased by up to 59 times fasting levels. Magnitudes of many of these responses (O_2 consumption rate, kidney hypertrophy, and D-glucose and L-lysine uptake) increased with meal size up to the largest meals studied; other responses (Na^+-independent L-leucine uptake, plasma Cl^-, and organ masses) plateaued at meals equal to 25% of the snake's body mass; and still other responses (nutrient uptake at *day 1*, passive glucose uptake, and plasma protein and alkaline phosphatase) were all-or-nothing, being independent of meal size between 5 and 65% of body mass. Pythons undergo a wide array of postprandial responses, many of which differ in their sensitivity to meal size.

blood chemistry; intestinal hypertrophy; intestinal nutrient transport; specific dynamic action

VERTEBRATE DIGESTIVE SYSTEMS adapt in mass and in enzyme and transporter activities to dietary composition and food intake rates (12, 14). For example, mouse small intestine doubles its brush-border glucose transporter activity after a switch from a carbohydrate-free to a high-carbohydrate diet (5), and it doubles its mass and hence its brush-border glucose transporter capacity with the fourfold increase in food intake rate at peak lactation (8). Although these adaptive responses are physiologically important, their scope is nevertheless modest in mice and other mammalian species studied to date, because most mammals are adapted to consuming relatively small meals at short intervals, hence dietary loads on the gut vary only modestly with time.

Much greater variations in dietary loads and hence in digestive responses are encountered in sit-and-wait foraging snakes, which are adapted to consuming relatively huge meals at long intervals (23). For instance, to a rattlesnake or python a normal meal is a prey animal with a mass 25% of the snake's own body mass at intervals of ~1 mo (25, 29). That meal size produces a reversible 4- to 24-fold increase in brush-border nutrient transporter capacities (23, 26). The downregulation of intestinal mass and activities after completion of digestion serves to minimize the energetic cost of maintaining the gut during the long interval between meals (23, 26).

Although pythons thus typically consume relatively larger meals and exhibit larger intestinal regulatory scopes than mice, does regulatory scope increase with meal size for pythons themselves? One hint comes from studies of the increased whole animal metabolic rate [rate of O_2 consumption ($\dot{V}O_2$)] accompanying feeding, also known as specific dynamic action (SDA, see Ref. 17). We recently observed that the magnitude of SDA increases with meal size in pythons (24). If the cost of intestinal upregulation contributes significantly to SDA, our SDA measurements would suggest larger regulatory scopes with larger meals. However, it is also possible that the ingestion of any meal above some minimal size triggers similar magnitudes of regulatory response in pythons.

To answer this question, we have now studied the magnitude and duration of adaptive responses in pythons that consumed meals equivalent to 5, 25, or 65% of their body mass. We already noted that the large digestive responses of sit-and-wait foraging snakes make them ideal models for analyzing mechanisms of gastrointestinal adaptation (23, 26). If even larger responses could be obtained from snakes consuming meals larger than the 25% meals studied previously, that would further increase the value of snakes as a gastrointestinal model species. We are not concerned with setting a record for the sake of the record itself: modest response magnitudes have seriously limited progress in gastrointestinal research. For example, it took the development of a sheep model in which brush-border glucose transporter activity increased 80-fold, instead of the twofold increase attainable in mice, before the mechanism of glucose transporter upregulation could be conveniently studied at the molecular level (28). We shall show that responses in snakes do increase with meal size, and consequently we have now begun to use large meals (65% of body mass) in our ongoing studies of underlying hormonal mechanisms (e.g., Ref. 1).

MATERIALS AND METHODS

Animals and Their Maintenance

We purchased hatchling Burmese pythons (*Python molurus*) weighing ~100 g from a commercial breeder (Captive Bred Reptiles, Oklahoma City, OK) and maintained them on

biweekly meals of mice or rats with water available ad libitum. We found these pythons to complete digestion within 10–14 days postfeeding and to defecate within the following week (23). Hence, before feeding a snake to obtain measurements, we first fasted the snake for 1 mo to ensure that it was initially in a postdigestive state. Snakes were then fed one to three juvenile or subadult rats of mass equal to 5, 25, or 65% of the snake's body mass before feeding and thereafter were maintained at 30°C in an environmental chamber during metabolic measurements or until death.

Our study used 54 pythons [mean body mass 734 ± 33 (SE) g at the time of study], of which 24 (mean body mass 684 ± 62 g) were not killed but were used to measure the metabolic response (see below). These 24 snakes were divided equally (8 snakes each) among the three meal size treatments, such that there was no significant [$F(2,21) = 0.01$, $P = 0.99$] difference in body mass among meal size treatments. The remaining 30 snakes (mean body mass 773 ± 31 g) were killed by severing the spinal cord immediately posterior to the head to measure rates of digestion, blood chemistry, organ masses, and intestinal nutrient uptakes. Of those 30 snakes, one set of three was killed after a 30-day fast. The other 27 snakes were divided equally (9 snakes each) among the three meal size treatments, with three snakes for each meal size treatment killed at 1, 3, or 6 days after feeding. Thus sample size was three snakes for each meal size-and-time treatment. Mean body mass did not differ significantly [$F(9,20) = 0.10$, $P = 0.99$] among these 10 samples of three snakes each.

Metabolic Response to Feeding

We measured the O_2 consumption rate ($\dot{V}O_2$) of pythons before and after meal ingestion by closed-system respirometry (described in Refs. 26, 31). Briefly, $\dot{V}O_2$ was calculated from the 0.25–1 h depletion of O_2 by a python within a respirometry chamber maintained at 30°C. O_2 content of chambers did not drop below 18%, and CO_2 content did not rise above 2.5%, changes of which we have observed to have no effect on pythons. $\dot{V}O_2$ was corrected for standard temperature and pressure and is reported as milliliters O_2 per gram per hour. Snake body mass and volume were recalculated daily to account for the respective changes due to growth and digestion. We measured $\dot{V}O_2$ daily [0600–0800 Pacific standard time (PST)] for 2 days before feeding to determine the snake's standard metabolic rate (SMR), then we measured $\dot{V}O_2$ at 12- to 24-h intervals after feeding (0600–0800, 1800–2000 PST) for 7–17 days, depending on meal size. For each meal size treatment we designated the period that postprandial $\dot{V}O_2$ significantly exceeded prefeeding $\dot{V}O_2$ as the duration of the metabolic response. We determined for each snake its SMR (lowest $\dot{V}O_2$ measured before feeding), peak $\dot{V}O_2$ (highest $\dot{V}O_2$ measured after feeding), scope of peak $\dot{V}O_2$ (defined as peak $\dot{V}O_2$/SMR), average $\dot{V}O_2$ for the duration of the metabolic response, and the total magnitude of the postprandial response (SDA). We quantified SDA alternatively as *1*) the extra O_2 consumed (above SMR) during the duration of the metabolic response; *2*) energy (in kJ) expended (assuming a conversion factor of 19.8 J/ml of extra O_2 consumed, see Ref. 7); and *3*) proportion of energy ingested (assuming a conversion factor of 8 kJ/g wet mass of rodent, see Ref. 23).

Rate of Digestion

We measured rate of digestion for each meal size by weighing gut contents from killed snakes. The stomach and small intestine were removed, weighed, flushed of their contents, and reweighed. The difference in organ mass before and after flushing was taken as the mass of the organ's content, and was reexpressed as a percentage of the wet mass of the ingested meal.

Blood Chemistry

Blood (2–3 ml), drawn from each snake's heart at the time of death, was centrifuged for 10 min at 4,000 revolutions/min at 4°C. The plasma was analyzed (Hitachi Blood Analyzer model 747) for concentrations of Na^+, K^+, Cl^-, Ca^{2+}, phosphorus, CO_2, glucose, creatinine, total protein, urea blood nitrogen, albumin, and alkaline phosphatase.

Organ Masses

To assess effects of meal size on intestinal hypertrophy, we first measured the wet mass of the whole small intestine and separately its anterior two-thirds and distal one-third (hereafter referred to as anterior and distal small intestine). We next measured the wet mass of scrapeable mucosa and residual serosa from a 1-cm sleeve taken from each small intestinal region, dried the mucosal and serosal samples to constant weight at 60°C, and thereby calculated regional and total small intestinal mucosal and serosal dry masses (5). Because we had observed other organs to change in mass with feeding and digestion (22, 23), we also measured the wet and dry masses of the paired lungs, heart, liver, empty stomach, full gallbladder, pancreas, large intestine, and paired kidneys.

Intestinal Nutrient Uptake

We measured in vitro nutrient uptake rates across the intestinal brush-border membrane (see Refs. 13, 26 for details). Briefly, after we severed the spinal cord, the small intestine was removed, weighed, flushed with ice-cold Ringer solution, everted, divided into equal-length thirds, and cut into 1-cm sleeves. Sleeves were mounted on glass rods and first incubated for 5 min in Ringer solution at 30°C and then incubated for 2 min at 30°C in a Ringer solution containing a radiolabeled nutrient and an adherent fluid marker labeled with a different radioisotope. We thereby measured intestinal uptake rates of the amino acids L-aspartate, L-leucine, L-lysine, and L-proline (each at 50 mmol and labeled with ^3H) and of the sugars L-glucose (at trace concentrations and labeled with ^3H) and D-glucose (at 20 mmol and labeled with ^{14}C). We selected these four amino acids because each is transported predominantly by one of the following major intestinal amino acid carriers: the acidic, neutral, basic, and imino acid transporter, respectively (30). To correct for the amount of radiolabeled nutrient in the fluid adherent to the intestine, we used a second labeled solute, [^{14}C]polyethylene glycol for the amino acids and L-glucose and L-[^3H]glucose for D-glucose. In addition, L-[^3H]glucose corrects for D-glucose transported via passive diffusion. Hence, we measured total uptake (carrier-mediated plus passive) of each amino acid, passive uptake of L-glucose (which is not transported by a carrier), and carrier-mediated uptake of D-glucose. We express uptake rates as nanomoles per minute per milligram of sleeve wet mass.

In addition, we measured Na^+-independent uptake of L-leucine and L-proline by preincubating and incubating sleeves in solutions in which NaCl had been isosmotically replaced with choline chloride. Na^+-dependent uptake was calculated by subtracting Na^+-independent uptake from total uptake (as measured in normal Na^+-containing Ringer solution). Our selection of incubation time and temperature, solute concentration, and solution composition arose from validation experiments (see Ref. 26 for details).

We measured regional uptake rates of each solute from each one-third of the small intestine (proximal, middle, and

distal). In addition, we measured the uptake rate of L-leucine, L-proline, and D-glucose from the proximal one-half of the large intestine. As described previously (23), we calculated the total small intestinal uptake capacity (μmol/min) for each nutrient by summing the products of regional nutrient uptake rate ($nmol \cdot min^{-1} \cdot mg^{-1}$) times regional mass (mg).

Statistical Analyses

We used a repeated-design analysis of variance (ANOVA) to test for a significant effect of sampling time (before and after feeding) on metabolic rate. A repeated-design ANOVA was also employed to test for positional effects (proximal, middle, and distal small intestine and large intestine) on nutrient uptake rates. To test for treatment effects (meal size or meal size-and-time), we carried out three analyses: *1*) ANOVA on treatments, *2*) analysis of covariance (ANCOVA) with body mass as a covariate, and *3*) ANCOVA to test for the interaction between treatment and body mass (34). For the variables SMR, peak $\dot{V}O_2$, scope of peak $\dot{V}O_2$, SDA as a percent of ingested kilojoules, nutrient uptake rates, and blood chemistry, the first ANCOVA showed body mass not to be a significant covariate, hence we report the results of the ANOVA. For the variable SDA as extra O_2 consumed or as kilojoules expended, body mass proved to be a significant covariate ($P < 0.05$), but there was a significant interaction between body mass and treatment; hence we again report the ANOVA results. For the uptake capacities and organ masses, body mass proved to be a significant covariate and there was no significant interaction between body mass and treatment; hence we report the results of the first ANCOVA.

In conjunction with ANOVA or ANCOVA, we made a priori planned pairwise mean comparisons between pairs of treatments. We refer to overall effects of treatment as "a difference among treatments," and we refer to differences between pairs of treatments as "a difference between treatments." Whenever ANOVA or ANCOVA and all pairwise comparisons proved significant, we refer to "significant differences among and between treatments." Throughout the text we report results of ANOVA and ANCOVA in terms of their F and P values, and we provide P values of significant pairwise comparisons. We designate the level of statistical significance as $P < 0.05$. Mean values are reported either as means ± SE or as means adjusted for effects of body mass (least-squares means from ANCOVA ± SE). We conducted all statistical analyses by the microcomputer version of SAS (21).

RESULTS

Metabolic Response to Feeding

Standard metabolic rates of the 24 pythons used to measure postprandial metabolism averaged 0.036 ± 0.001 ml $O_2 \cdot g^{-1} \cdot h^{-1}$. As expected (because SMR was measured before feeding), we found no significant difference in individual SMR among the three meal size treatments [ANOVA, $F(2,21) = 1.00$, $P = 0.39$] nor between pairs of meal size treatments (pairwise comparisons, P values ≥ 0.17) (Table 1). $\dot{V}O_2$ increased rapidly after feeding, such that within 12 h postfeeding it had increased significantly (P values ≤ 0.0001) to values 2, 6, and 8.5 times SMR, respectively, for the 5, 25, and 65% meals (Fig. 1). $\dot{V}O_2$ continued to increase and peaked at 24 h postfeeding, at average values of 5, 15, and 32 times SMR for the three respective meal sizes. Peak $\dot{V}O_2$ and the scope of peak $\dot{V}O_2$ differed significantly (P values ≤ 0.0001) among and between meal sizes (Table 1). After the peak at 24 h, $\dot{V}O_2$ declined significantly (P values ≤ 0.0002) by *day 2* and again by *day 3* for each meal size. For pythons that consumed 5, 25, and 65% meals, $\dot{V}O_2$ returned to values not significantly greater than those before feeding by *days 4*, *8*, and *13*, respectively. At every sampling time from 0.5 to 10 days postfeeding, $\dot{V}O_2$ differed significantly (P values < 0.004) between meal size treatments in the order 5% < 25% < 65% meals.

Meal size also affected the time-averaged $\dot{V}O_2$ and the extra O_2 consumed or energy expended above SMR during the days of significantly elevated rates (Table 1). $\dot{V}O_2$ averaged over the days of the metabolic response

Table 1. *Metabolic response of pythons to ingestion of meals equal in mass to 5, 25, or 65% of the snake's body mass*

Variable	Meal Size, %			ANOVA	
	5	25	65	F	P
n	8	8	8		
Body mass, g	676 ± 125	694 ± 136	680 ± 62	0.01	0.994
Meal mass, g	34 ± 6	174 ± 34	424 ± 40	45.9	0.0001
Meal mass, %	5.1 ± 0.04	25.0 ± 0.01	65.0 ± 0.11		
SMR	0.038 ± 0.002	0.036 ± 0.002	0.034 ± 0.001	1.0	0.386
Peak $\dot{V}O_2$	0.19 ± 0.02	0.55 ± 0.04	1.05 ± 0.06	93.8	0.0001
Scope	5.1 ± 0.3	15.8 ± 1.4	31.6 ± 2.0	91.3	0.0001
Duration	4	8	13		
Average $\dot{V}O_2$	0.11 ± 0.01	0.20 ± 0.02	0.32 ± 0.01	182.9	0.0001
SDAs					
O_2 consumed	3,820 ± 540	21,400 ± 4,250	64,600 ± 6,530	48.1	0.0001
kJ expended	76 ± 11	424 ± 84	1,280 ± 130	48.1	0.0001
% of ingested energy	29.4 ± 2.0	30.1 ± 1.2	36.0 ± 1.4	5.5	0.012

Values are means ± SE, except for duration (n = no. of snakes). Fourth row is meal mass as a percentage of snake body mass. SMR, standard metabolic rate, measured after snake had been fasted for 30 days; peak $\dot{V}O_2$, peak O_2 consumption rate after feeding; scope, ratio of peak $\dot{V}O_2$ to SMR; duration, no. of days after feeding during which $\dot{V}O_2$ was significantly elevated over fasting levels; average $\dot{V}O_2$, time-averaged $\dot{V}O_2$ over duration of significantly elevated $\dot{V}O_2$. Units of SMR, $\dot{V}O_2$, and average $\dot{V}O_2$ are ml $O_2 \cdot g^{-1} \cdot h^{-1}$. Specific dynamic action (SDA) is expressed as total extra ml O_2 consumed over duration of elevated $\dot{V}O_2$, the energy equivalent (kJ) of that energy expenditure as a percentage of energy content of ingested meal. F and P values from analysis of variance (ANOVA) illustrate statistical significance of meal size effects on each variable.

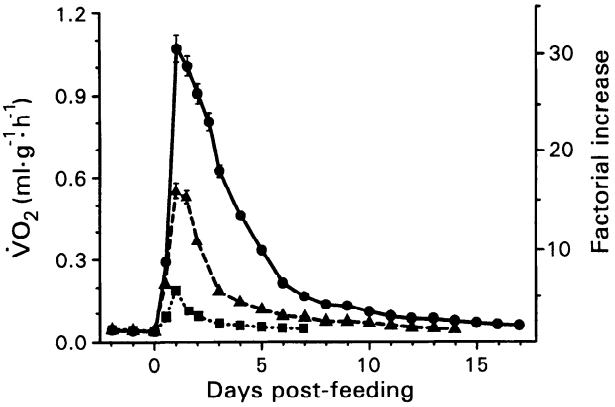

Fig. 1. Mean O_2 consumption rates ($\dot{V}O_2$) of pythons (n = 8 for each meal size treatment) for 2 days before and up to 17 days after ingestion of meals equal in mass to 5% (■), 25% (▲), or 65% (●) of the snake's body mass. *Right* axis depicts factorial increase in $\dot{V}O_2$ over fasting values. In this and subsequent figures, vertical bars represent ± SE and are omitted if SE is smaller than symbol for mean value. Note that both peak $\dot{V}O_2$ and duration of elevated $\dot{V}O_2$ increase with meal size.

differed significantly (P values ≤ 0.0001) among and between meal sizes (Table 1). During the 4, 8, and 13 days, respectively, for the 5, 25, and 65% meals, time-averaged $\dot{V}O_2$ equaled, respectively, 2.8, 5.5, and 9.4 times SMR. The extra O_2 consumed (above SMR) over the duration of digestion also increased with meal size (Table 1), such that snakes that had eaten the 25 or 65% meals consumed, respectively, 5.6 or 17 times more O_2 than snakes that had eaten the 5% meals. The energy equivalent (kJ) of the extra O_2 consumed (SDA) also increased with, and differed (P values < 0.012) among and between, meal sizes (Table 1). The energy equivalent of SDA averaged 32 ± 1% of the ingested energy for all 24 snakes combined, although this proportion was significantly greater (P values < 0.014) for 65% meals (36 ± 1%) than for 25% (30 ± 1%) or 5% (29 ± 2%) meals (Table 1).

In short, $\dot{V}O_2$ rose to a higher peak value, remained elevated for longer, and represented a greater fraction of the energy in the ingested meals as meal size increased.

Rate of Digestion

Digestion of smaller meals was completed more rapidly than larger meals (Fig. 2). Thus, within 1 day of feeding, the proportion of the ingested meal mass that had passed out of the stomach was 74 ± 7% for the 5% meal, but only 27 ± 2 or 21 ± 2% for the 25 or 65% meals, respectively. At *day 3* the 25 and 65% snakes had significantly (P values < 0.0001) reduced stomach contents further, to 27 ± 7 and 40 ± 8% of ingested meal mass, respectively, but stomachs of 5% snakes were already completely empty. By *day 6* the small intestine was also empty in the 5% snakes but still contained food (5 ± 2 or 4 ± 1% of meal mass, respectively) in the 25 or 65% snakes. From meal mass and mass of stomach contents, we calculate that food exit rates from the stomach to the small intestine averaged 1.9, 2.3, and 4.3 g/h for 5, 25, and 65% snakes, respectively.

Blood Chemistry

Except for plasma concentrations of total protein [$F(9,20)$ = 0.41, P = 0.92] and alkaline phosphatase [$F(9,20)$ = 3.89, P = 0.06], plasma concentrations of all solutes analyzed varied significantly among meal size-and-time treatments [$F(9,20)$ values from 3.0 to 28.1, P values < 0.02] (Fig. 3).

The most striking changes (11–18 mM) were the reciprocal decrease in Cl^- and increase in CO_2 in 25 and 65% snakes within 24 h postfeeding. Plasma glucose, creatinine, and urea nitrogen rose by 2.3- to 4-fold in 65% snakes at *day 1* and then declined to fasting levels. Plasma phosphorus concentration rose at *day 1* for snakes consuming all meal sizes and remained elevated at *days 3* and *6* for the two larger meals. Changes in plasma Na^+, K^+, Ca^{2+}, and albumin were smaller but still statistically significant.

Organ Masses

Small intestinal mass. Measures of small intestinal wet mass were elevated from *days 1* to *6* for snakes consuming the two larger meals (Fig. 4). The whole intestinal mass doubled in the anterior small intestine and increased by 60% in the distal small intestine. When the whole intestine was resolved into its mucosal and serosal components, there were changes in both components, but the relative increases in the mucosa exceeded those in the serosa. The largest change was in the anterior mucosa, which increased in mass by 2.4-fold. The distal mucosa and anterior serosa also increased, but changes in the distal serosa failed to achieve significance. Increases in dry masses were generally similar to those in wet mass, except that the changes in the distal mucosa and anterior serosa no longer achieved significance.

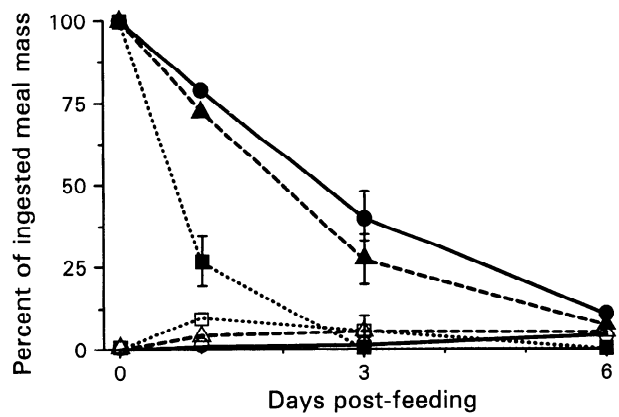

Fig. 2. Percentage of ingested meal remaining within stomach (closed symbols) and small intestine (open symbols) at 1, 3, and 6 days after ingestion of meals equal in mass to 5 (■, □), 25 (▲, △), or 65% (●, ○) of the snake's body mass. In this and all subsequent figures, n = 3 for each meal size-and-time treatment. Note that the smallest meal is digested more rapidly than the 2 larger meals, as gauged by more rapid food entry into the small intestine and more rapid emptying of stomach and then of the small intestine.

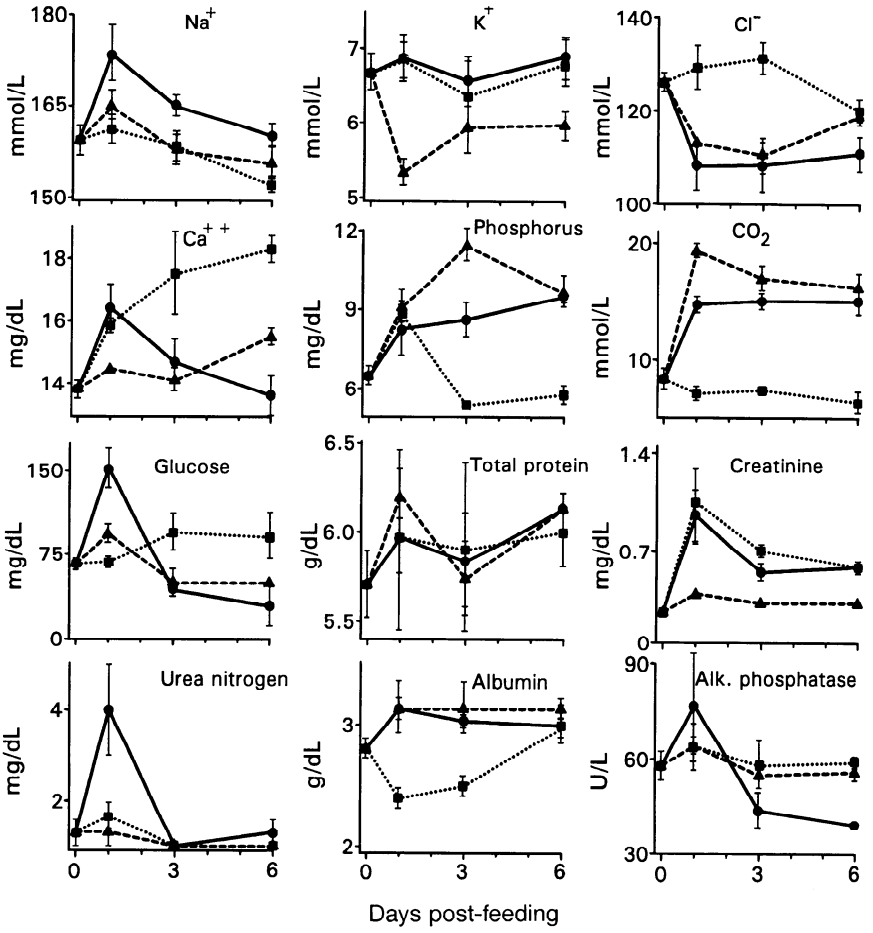

Fig. 3. Plasma solute levels at *day 0* (i.e., fasted) and at 1, 3, and 6 days after ingestion of meals equal to 5 (■), 25 (▲), or 65% (●) of snake's body mass. In this and subsequent figures, fasted values are from snakes 30 days after ingestion of last meal. Note significant postfeeding changes in Cl^-, glucose, creatinine, and urea nitrogen.

Other organs. Among organs other than the small intestine, wet mass increased with feeding for all except the lungs and large intestine in snakes consuming the two larger meals (Fig. 5). Masses of the paired kidneys, liver, pancreas, and stomach were generally elevated from *days 1* to *6* and peaked on *day 3* at values ~105, 54, 28, and 22% above the respective fasting values. Heart mass showed a small but significant increase, whereas mass of the gallbladder plus its contents decreased (due to discharge of bile into the small intestine). Changes in dry mass were generally similar to these changes in wet mass.

Intestinal Nutrient Uptake

Positional effects. Among almost all measured nutrients, we found significant effects of intestinal position on uptake rates for each meal size treatment. Uptake rates in the proximal and middle regions of the small intestine were statistically indistinguishable in 57 of 70 cases, whereas uptake rates in the distal small intestine were significantly less than those in either the proximal or middle regions in 24 of 70 cases. Uptake rates in the large intestine were significantly less than those in small intestinal regions for 80% of the comparisons. For example, at 6 days postfeeding, uptake rates in the distal small intestine averaged 57–69% of rates in the proximal and middle regions, and uptake rates in the large intestine averaged 25–40% of rates in the distal small intestine. Hence we averaged rates from the proximal and middle regions and hereafter refer to this combined region as the anterior small intestine.

Meal size-and-time effects. Uptake rates in the anterior small intestine (Fig. 6) differed significantly among meal size-and-time treatments for all solutes [$F(9,20) = 4.22$ to 55.5, P values < 0.004]. At 1 day postfeeding, uptake rates of all nutrients had significantly (P values < 0.002) increased above fasting values, but without significant (P values > 0.24) differences between meal size treatments. Effects of meal size appeared after *day 1*, as rates continued to increase for the largest meal but declined for the smallest meal. Snakes that had consumed 5% meals downregulated uptakes of L-leucine and L-proline back to fasting levels by *day 3* and uptakes of the other three solutes (L-aspartate, L-lysine, and D-glucose) by *day 6*. Snakes that had consumed 25% meals exhibited at *day 3* no change in uptake of any solute from *day 1* peak values and downregulated uptakes of L-leucine and L-proline, but not of the other three solutes, to fasting values by *day 6*. Snakes that had consumed 65% meals exhibited further significant (P values < 0.0001) increases of L-lysine and D-glucose uptakes (no significant changes for the other three solutes) above *day 1* values by *day 3*. For this meal size all solutes continued to have uptakes significantly (P values ≤ 0.0003) elevated above fasting values at *day 6*, with L-lysine and D-glucose uptake

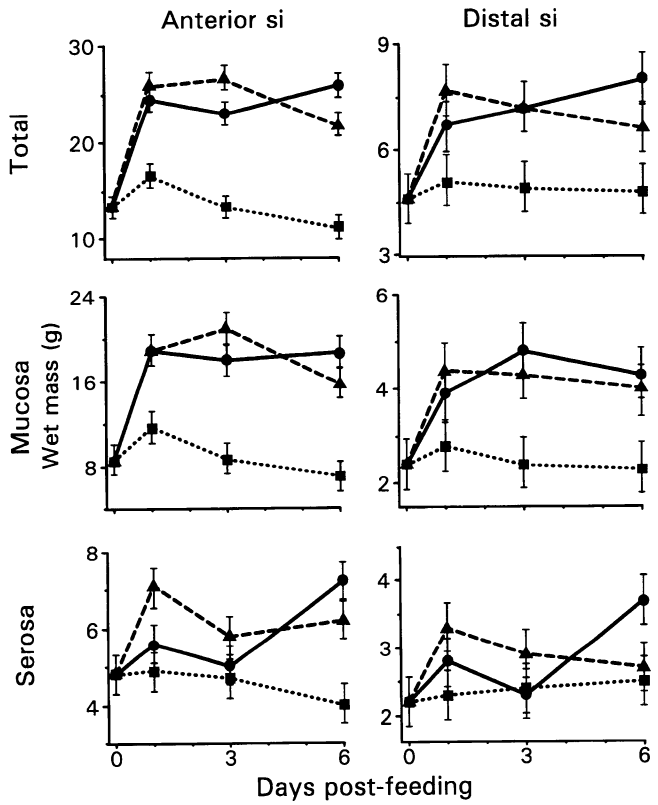

Fig. 4. Wet mass (g) of whole anterior and distal small intestine (si) and of its separate mucosal and serosal components at *day 0* (i.e., fasted) and at 1, 3, and 6 days after ingestion of meals equal to 5 (■), 25 (▲), or 65% (●) of the snake's body mass. Note lack of a mass change after ingestion of the 5% meal and the mass increase of the serosa and the mucosa after ingestion of the 2 larger meals.

declining significantly (P values ≤ 0.0001) below *day 3* values. For snakes consuming 65% meals, peak factorial increases in uptake rates of L-aspartate, L-leucine, L-lysine, L-proline, and D-glucose by anterior small intestine were at values 11, 8, 14, 10, and 41 times their respective fasting values and occurred on *days 1, 3, 3, 6,* and *3*, respectively.

Although absolute uptake rates in the distal small intestine were somewhat lower than those in the anterior small intestine, the stimulatory effects of feeding were similar, with minor differences of detail (Fig. 6). At *day 1* after feeding, uptake rates of all amino acids at all meal sizes had significantly (P values ≤ 0.048) increased above fasting values, whereas uptake rates of D-glucose remained unchanged. Differences in uptake as a function of meal size had already appeared at *day 1* for L-proline, as 65% snakes had significantly ($P = 0.006$) higher rates than 5% snakes. Amino acid uptakes by 5% snakes declined back to fasting levels by *day 3*, whereas uptakes by 25 and 65% snakes were still significantly elevated (except for L-aspartate uptake by 25% snakes). At this time, D-glucose uptake rates were now significantly elevated (P values < 0.003) in both 25 and 65% snakes. By *day 6*, uptakes by 25% snakes had returned to fasting levels for all solutes except D-glucose ($P = 0.004$), whereas uptakes by 65% snakes were still significantly elevated for all solutes except L-aspartate. For 65% snakes, peak factorial increases in distal intestinal uptake rates of L-aspartate, L-lysine, L-proline, and D-glucose were at values 43, 26, 5, and 6 times their respective fasting values and occurred on *day 3*, *3*, *1*, and *3*, respectively. The peak factorial increase for L-leucine, at six times fasting values, also occurred on *day 3* but in 25% rather than in 65% snakes.

The large intestine experienced significantly (P values ≤ 0.024) elevated uptakes at *day 1* for L-leucine by 5 and 25% snakes and at *day 3* for L-proline by 25 and 65% snakes (Fig. 6). Peak factorial increases within the large intestine for L-leucine, L-proline, and D-glucose occurred at *day 1* in 5% snakes, *day 1* in 65% snakes, and *day 3* in 25% snakes, to levels four, six, and two times fasting values, respectively.

Uptake capacities. The uptake capacity of the entire small intestine of each nutrient (integrated product of regional uptake rates and masses) (Fig. 7) increased with days postfeeding and meal size [$F(9,20) = 7.78$ to 32.1, P values < 0.0001], because of the increased uptake rates (Fig. 6) and increased small intestinal masses (Fig. 4). Capacities for all nutrients at all meal sizes were significantly (P values ≤ 0.049) elevated above fasting values by *day 1*. Capacities of 5% snakes returned to fasting values for L-lysine by *day 6* and for the other solutes by *day 3*, but capacities of 25 and 65% snakes for all nutrients were still significantly elevated

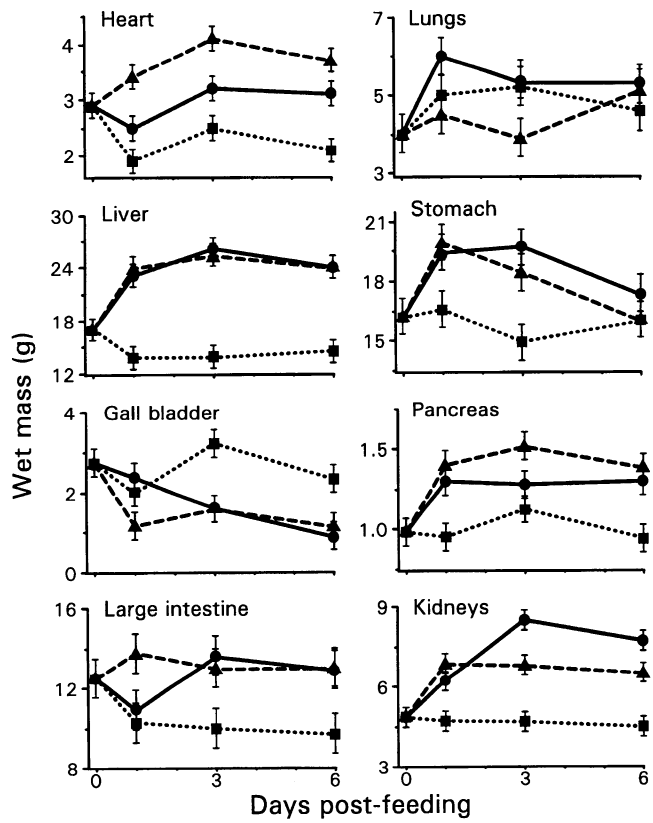

Fig. 5. Wet masses (g) of various organs (gallbladder, full gallbladder including contents; kidneys, both kidneys combined) at *day 0* (i.e., fasted) and at 1, 3, and 6 days after ingestion of meals equal to 5 (■), 25 (▲), or 65% (●) of the snake's body mass. Note postfeeding mass changes for most organs, except the lungs and large intestine, for 25 and 65, but not 5% meals.

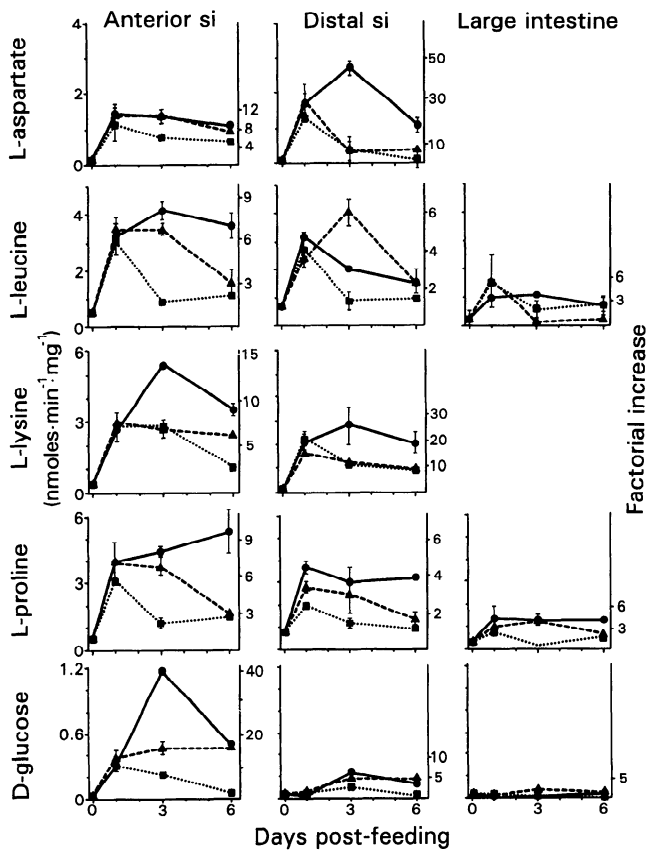

Fig. 6. Intestinal brush-border uptake rates (nmol·min^{-1}·mg^{-1}) of 5 nutrients by the anterior and distal small intestine at *day 0* (i.e., fasted) and at 1, 3, and 6 days after ingestion of meals equal to 5 (■), 25 (▲), or 65% (●) of the snake's body mass. Uptake rates of L-leucine, L-proline, and D-glucose are also illustrated for the large intestine. *Right* axis illustrates factorial increase in uptake rates over fasting values. Note that uptake rates are upregulated by *day 1* but that they generally do not vary with meal size until *day 3*.

at both *day 3* and *day 6*. Capacities of 25 and 65% snakes significantly (P values < 0.042) exceeded those of 5% snakes for three nutrients (L-leucine, L-lysine, and L-proline) already by *day 1*, whereas capacities of 65% snakes significantly (P values ≤ 0.038) exceeded those of 25% snakes at *day 6* for all amino acids. Peak values of capacities were attained in 65% snakes at *day 3* for most solutes (*day 6* for L-proline), at values 26, 14, 32, 59, and 16 times fasting values for L-aspartate, L-leucine, L-lysine, D-glucose, and L-proline, respectively.

Na^+-independent and Na^+-dependent amino acid uptake. Both Na^+-independent and Na^+-dependent uptake of both L-leucine and L-proline in the anterior small intestine varied significantly [$F(9,20) = 4.38$ to 22.2, P values ≤ 0.003] with meal size and time (Fig. 8). Na^+-independent uptakes of L-leucine and L-proline were significantly (P values ≤ 0.033) elevated above fasting values at all meal sizes and times except for 5% snakes at *day 3* (L-leucine and L-proline) and *day 6* (L-leucine). Na^+-dependent uptakes were significantly elevated for 65% snakes at *days 3* and *6* (not at *day 1*), but for 25 and 5% snakes at *day 1*, *3*, or *6* in only 2 of 12 possible cases. Factorial peaks were 42 (Na^+-dependent L-leucine), 41 (Na^+-dependent L-proline), 9 (Na^+-independent L-proline), and 5 (Na^+-independent L-leucine) times fasting values, respectively, for 65 (*day 6*), 65 (*day 3*), 25 (*day 3*), and 65% (*day 1*) snakes.

There were no significant effects of 5% meals on distal intestinal Na^+-independent or Na^+-dependent uptake of L-leucine or L-proline at any day, except for Na^+-independent L-leucine uptake at *day 1* (Fig. 8). Significant effects of 25 and 65% meals were mostly confined to *days 1* and *3*. Factorial peaks were 10 (Na^+-dependent L-leucine), 10 (Na^+-dependent L-proline), 5 (Na^+independent L-proline), and 5 (Na^+-independent L-leucine) times fasting values, respectively, for 25 (*day 3*), 65 (*day 3*), 65 (*day 1*), and 65% (*day 1*) snakes.

The Na^+-independent component contributed >50% of total uptake of both L-leucine and L-proline in both the anterior and distal small intestines at all three meal sizes and all three times, except for a slight preponderance [51 and 62% of the Na^+-dependent component for L-proline uptake in two of nine possible cases in the anterior small intestine (Fig. 8)]. Nevertheless, as detailed in the preceding two paragraphs, the largest factorial increases associated with feeding were in the smaller Na^+-dependent component.

Passive glucose uptake. The mean passive permeability coefficient of glucose (K_p), calculated from L-glucose

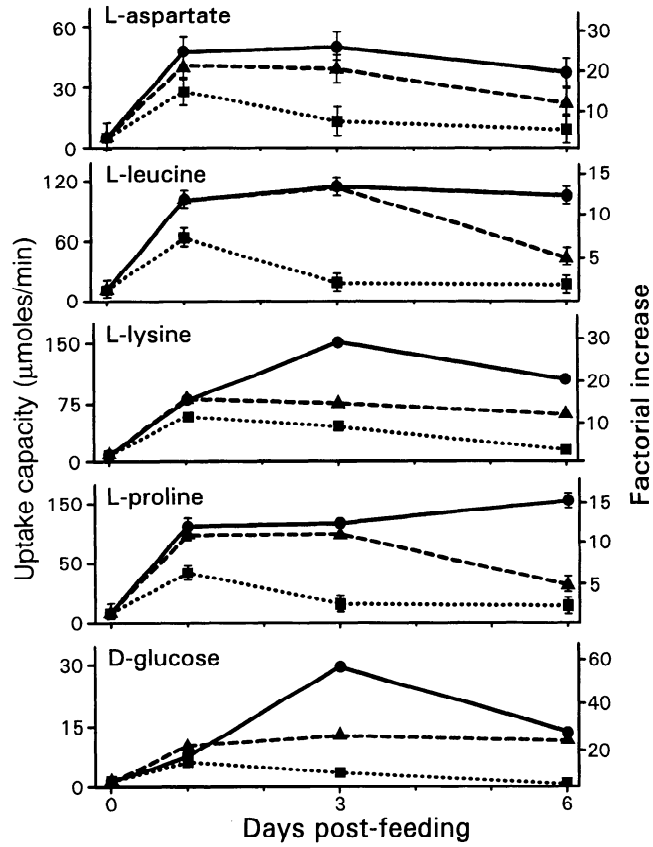

Fig. 7. Total intestinal uptake capacities μmol/min) of 5 nutrients at *day 0* (i.e., fasted) and at 1, 3, and 6 days after ingestion of meals equal to 5 (■), 25 (▲), or 65% (●) of the snake's body mass. *Right* axis illustrates factorial increase in uptake capacities over fasting values. Note that uptake capacities are upregulated by *day 1*.

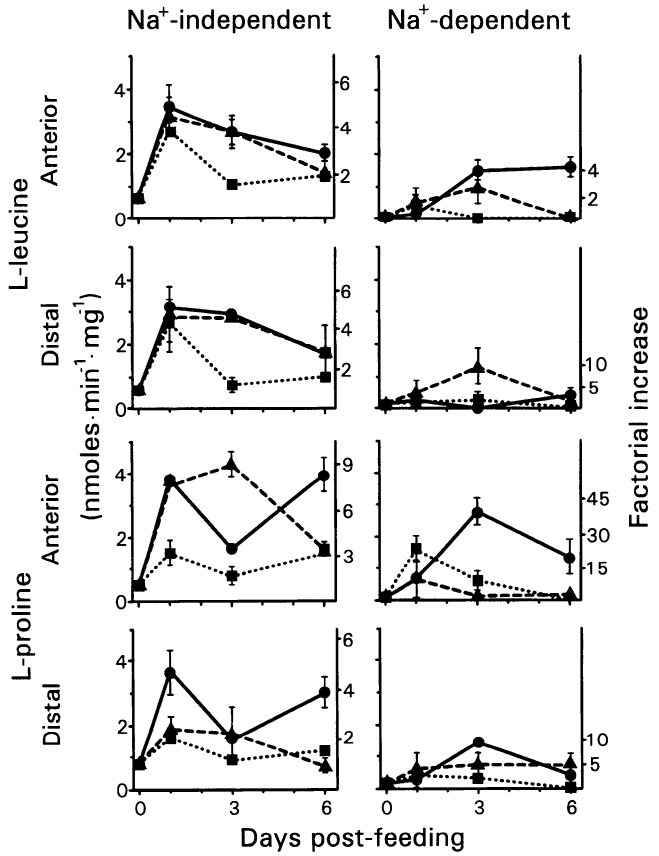

Fig. 8. Na^+-independent and Na^+-dependent components of L-leucine and L-proline brush-border uptake ($nmol \cdot min^{-1} \cdot mg^{-1}$) by anterior and distal small intestine at *day 0* (i.e., fasted) and at 1, 3, and 6 days after ingestion of meals equal to 5 (■), 25 (▲), or 65% (●) of the snake's body mass. *Left* axis scales are same for both components. *Right* axis illustrates factorial increase in uptake rates over fasting values. Note that Na^+-independent uptake generally exceeds Na^+-dependent uptake and that both components respond to feeding.

uptake rates of the anterior small intestine for all meal size-and-time treatments, was 0.009 ± 0.002 $\mu l \cdot min^{-1} \cdot mg^{-1}$ ($n = 30$) (Fig. 9). K_p of the anterior small intestine varied significantly [$F(9,20) = 6.46$, $P = 0.0003$] among meal size-and-time treatments. For all meal sizes, K_p of the small intestine increased significantly (P values ≤ 0.003) from fasting levels by *day 1* and then declined to values not significantly ($P > 0.012$) greater than fasting values by *day 3*. Because at *day 1* passive uptake was upregulated by a greater factor than was carrier-mediated D-glucose uptake, the percentage of total anterior D-glucose uptake that occurred via carrier-mediated transport was significantly ($P \leq 0.027$) lower at *day 1* than for fasting snakes or for fed snakes at *days 3* and *6* for all meal sizes (Fig. 9).

Uptake ratios. Most carnivorous animal species, because they are adapted to a diet high in protein and low in carbohydrate, have ratios of intestinal amino acid to D-glucose uptake >1.0, occasionally as high as 100 (15, 26). This proves also to be true for pythons for all four amino acids and all three meal sizes studied, in fasting snakes, and for all three times after feeding (Fig. 10). Because D-glucose uptake was upregulated by a greater factor than was any amino acid in the anterior small intestine, and because D-glucose uptake peaked at *day 3* (Fig. 6), amino acid-to-D-glucose uptake ratios reached minimal values of 1–5 at *day 3* for 65% snakes and reached peak values of 14–40 for fasting snakes and at *day 6* for 5% snakes.

DISCUSSION

We began this paper by asking whether pythons' adaptive responses to feeding vary with meal size. The results of this paper show that the answer to this question depends on the response considered. Responses whose magnitude increased continuously from 5 to 25 to 65% meals included the metabolic response ($\dot{V}O_2$), kidney hypertrophy, upregulation of nutrient uptake rates after *day 1*, and rises in plasma Na^+ and glucose. At the opposite extreme, the upregulation of uptake rates at *day 1* and of passive glucose uptake were virtually the same for all three meal sizes. An intermediate pattern consisted of only a slight or no response to 5% meals but nearly equally large responses to 25 and 65% meals, as observed for the deceleration of food passage rate, upregulation of Na^+-independent L-leucine uptake, decline of plasma Cl^-, and hypertrophy of the intestinal mucosa, liver, pancreas, and stomach. In the remaining response pattern, regardless of meal size, there was no change from fasting values (plasma protein and alkaline phosphatase). We shall now discuss each response in turn.

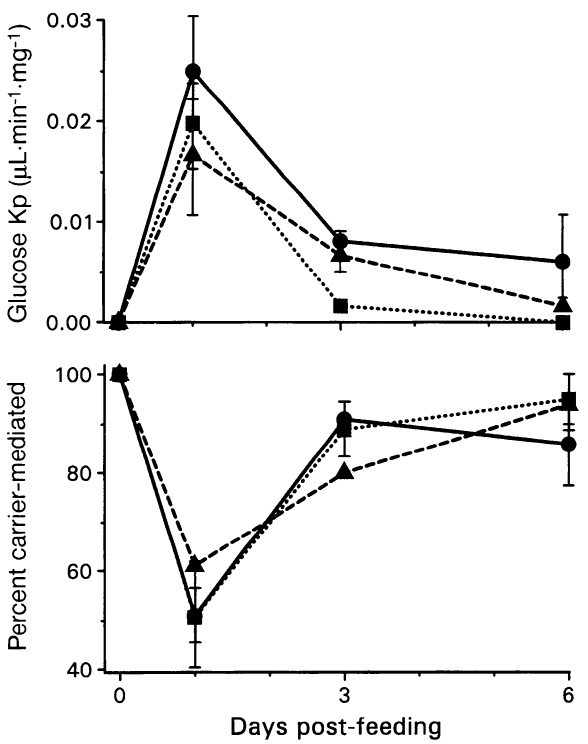

Fig. 9. Passive permeability coefficient of glucose (K_p) (*top*) and percentage of total glucose uptake that is carrier mediated (*bottom*) in anterior small intestine at *day 0* (i.e., fasted) and at 1, 3, and 6 days after ingestion of meals equal to 5 (■), 25 (▲), or 65% (●) of the snake's body mass. Note that passive uptake is transiently upregulated at *day 1* but that the carrier-mediated component predominates at other times.

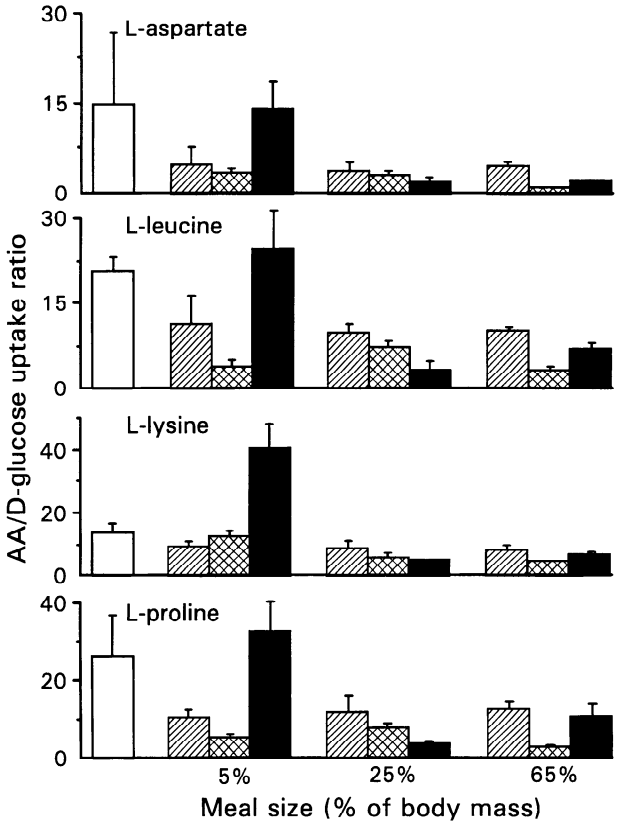

Fig. 10. Ratios of amino acid (AA) uptakes to D-glucose uptake for the anterior small intestine at *day 0* (i.e., fasted) (open bars) and at 1 (hatched bars), 3 (crosshatched bars), and 6 (filled bars) days after ingestion of meals equal to 5, 25, or 65% of the snake's body mass. Note that all ratios exceed 1.

Metabolic Response to Feeding

$\dot{V}O_2$ is one of the postprandial responses that increases with meal size. Peak $\dot{V}O_2$, the duration of elevated $\dot{V}O_2$, time-averaged $\dot{V}O_2$, and the extra energy expended during digestion (SDA) all increased with meal size in this study (Table 1). In another study we found them to increase over the whole range of meal sizes from 0 to 111% of python body mass (24). Qualitatively similar increases in postprandial $\dot{V}O_2$ with meal size have also been reported in other species of reptiles, birds, mammals, fish, and invertebrates (3, 4, 6, 9, 10).

The duration of food passage through python gut also increased with meal size and corresponded well to the duration of elevated $\dot{V}O_2$ (compare Figs. 1 and 2). For instance, pythons consuming 5% meals had digested 94% of that meal by *day 3*, and their $\dot{V}O_2$ correspondingly returned to fasting levels by *day 4*, whereas pythons consuming 25 or 65% meals still had food within both their stomach and their intestine at *day 6* and still had elevated $\dot{V}O_2$.

The scope of postprandial $\dot{V}O_2$ (peak $\dot{V}O_2$/SMR) in pythons of this study exceeds that for any other animal species and even exceeds the scope of peak $\dot{V}O_2$ during exercise for all vertebrates, with the exception of race horses (11). Contributing to their high postprandial scope, pythons possess low SMR (65% of predicted value in Ref. 2), consume large meals relative to body size (scope increases with relative meal size), and expend more energy digesting. Whereas other species, from cladocerans to humans, expend an equivalent of only 7–18% of ingested energy on SDA (10, 18, 32), pythons in the present study expended relatively the equivalent of 29–36%. This relatively high cost for pythons, and for other species of sit-and-wait foraging snakes, reflects the large expense of upregulating their previously quiescent organs to prepare them for the work of digestion (23, 26). For example, the estimated cost of small intestinal hypertrophy during the first 24 h after consuming a 25% meal is 33 kJ [assuming a cost of growth of 0.4 kJ/kJ of tissue (33) and an energy equivalent of tissue of 6.2 kJ/g wet mass (Secor and Diamond, unpublished data)], ~8% of SDA over the entire duration of digesting that meal.

This calculation illustrates one of the costs of upregulation, hence one of the factors contributing to the increase of SDA with meal size. Other contributions to SDA, from costly adaptive responses that we observed to differ between 5 and 65% snakes, include the following: greater hypertrophy of the liver, stomach, pancreas, large intestine, and kidneys (Fig. 5); more than 6 days versus 2 days of food residence in the stomach (Fig. 2), presumably implying a corresponding difference in the duration of continuous gastric HCl secretion, because we observed continuous HCl secretion during food residence in the stomach of snakes consuming 25% meals (Secor and Diamond, unpublished data); peristaltic propulsion and small intestinal absorption of 440 versus 34 g of ingested food; and synthesis of 180 versus 14 g of new python tissue (40% of 440 or 34 g), assuming a growth efficiency of 40% for pythons (24).

Blood Chemistry

One of the two most striking changes in blood chemistry on feeding was the precipitous drop in plasma Cl^- concentration within the first day (Fig. 3). Similar postprandial shifts, occurring with a reciprocal rise in HCO_3^-, have been observed in other species (4). They are due to gastric secretion of HCl, which depletes plasma Cl^- and results in accumulation of plasma HCO_3^- (because gastric H^+ secretion involves hydrolysis of H_2CO_3, with the H^+ secreted to the gastric lumen and the HCO_3^- extruded to the plasma in exchange for plasma Cl^-). This shift in Cl^- is undetectable in snakes consuming the smallest meal (5% of body mass), and had a larger duration in snakes consuming 65 than 25% meals (Fig. 3) because of the longer duration of gastric digestion with the largest meals (Fig. 2). The other striking change was the 90–140% postprandial increase in plasma CO_2 for the two largest meals (Fig. 3), due primarily to the before-mentioned accumulation of plasma HCO_3^- and secondarily to the increase in CO_2 production. Minor changes were the surge in plasma glucose during *day 1* after consumption of the largest meals, reflecting glucose mobilization from tissue stores to fuel gut rebuilding and the initial stages of digestion and the rises in phosphorus, creatinine, and urea nitrogen as metabolic end-products, reflecting increased metabolic rates.

Organ Masses

Many organs increased reversibly in mass to support the increased levels of functional activity accompanying the ingestion and digestion of the two larger meals (Figs. 4 and 5). The enlarged stomach carried out HCl secretion, muscular contractions, and maceration of the ingested rat; the enlarged small intestinal mucosa carried out enzymatic hydrolysis and nutrient uptake; the enlarged small intestinal serosa propelled the digesta by peristalsis; the enlarged pancreas produced digestive enzymes; the enlarged liver produced bile, metabolically transformed absorbed nutrients, and stored glycogen; and the enlarged kidney dealt with the increased load of metabolic wastes. The seemingly low demand of digesting the 5% meals is reflected in the general lack of organ hypertrophy. During the long fasts between meals, the python stomach, small intestine, and pancreas have virtually no work to perform, whereas the work load on the liver and kidneys is greatly reduced. Hence the atrophy of all these organs on completion of digestion (see Ref. 23) saves the snake maintenance costs, which are very high for several of these organs (19).

Intestinal Nutrient Uptake

The postprandial upregulation of small intestinal nutrient transport rates appears to be biphasic (Fig. 6). Within the first day, activities of all transporters examined are upregulated to levels independent of meal size, as an all-or-nothing response. In the second phase, through *days 3* and *6*, transporter activities are dependent on meal size. For example, pythons consuming the smallest meals (5% of body mass) downregulated some transporters to fasting levels by *day 3* and the other transporters by *day 6*; pythons consuming intermediate meals (25%) experienced no further transporter upregulation beyond *day 1* and downregulated some transporters between *days 3* and *6*. But pythons consuming the largest meals (65%) experienced further upregulation of several transporters between *day 1* and *day 3* and still maintained elevated activities above fasting levels for all transporters at *day 6*.

As already noted for small intestines of rattlesnakes, mice, and rabbits (16, 26, 30), python intestine possesses both Na^+-dependent and Na^+-independent mechanisms for amino acid uptake (Fig. 8). Passive diffusion may account for some of the Na^+-independent uptake, but some of it is likely to be carrier mediated, as hinted by its postprandial upregulation in pythons and suggested more strongly by its saturation kinetics and competition between amino acids in rattlesnakes, mice, and rabbits (16, 26, 30). Glucose passive permeability increased transiently at *day 1* as an all-or-nothing response independent of meal size (Fig. 9).

For 5% snakes the postprandial increases (2- to 13-fold) in nutrient uptake capacities (Fig. 7) are due entirely to increased uptake rates (per mg of intestinal tissue), because these snakes underwent no increase in small intestinal mass. However, for pythons consuming the two larger meals (25 and 65%), the large (up to 59-fold) increases in uptake capacities were a product of two factors: a smaller contribution from the twofold increase in small intestinal mass and a larger contribution from the up to 43-fold increase in uptake rates.

Adaptive Significance

At least three features of python digestive physiology serve to minimize energy expenditure by the snake. First, intestinal mass and transporter activities are downregulated after completion of digestion, thereby minimizing maintenance costs of the intestine during the unpredictably long fasting interval until the snake succeeds in capturing its next prey. This postdigestive atrophy of the intestine and of many other organs probably contributes to the low standard metabolic rates (measured in a postabsorptive state) of pythons and other species of sit-and-wait foraging snakes, whose standard metabolic rates are low, even when measured against other reptiles (2).

Second, as we have noted, many of pythons' responses to feeding are graded in magnitude according to meal size. As a result, the total metabolic expenditure associated with feeding (SDA) is almost directly proportional to meal size. In the wild, pythons consume a very wide range of meal sizes, from small to large mammals (20). Thus the observed proportionality of feeding-related energy expenditure to meal size means that pythons, in the face of the unpredictable variability in size of their natural meals, upregulate costly gut functions only to levels necessary for digesting the current meal.

Finally, both the upregulation and the downregulation of python intestine are rapid. Within 6 h of feeding, nutrient uptake rates increase as much as fourfold, and anterior intestinal mucosal mass increases by 50% (23). Within 1 day, total energy expenditure reaches a peak, and intestinal mass reaches a plateau. The time course of downregulation of transporter activities (Fig. 6), which varies with meal size, is similar to the time course of food passage through the gut at that meal size (Fig. 2). Thus the gut remains quiescent until prey is consumed, whereupon the gut is quickly upregulated, only to return to quiescence again when digestion is completed.

Perspectives

The examples of the squid axon, *Drosophila*, and *Necturus* illustrate the crucial contributions that especially favorable model species have made to our understanding of neurophysiology, population genetics, and kidney physiology, respectively. We proposed previously that pythons may prove similarly useful as a model species in gastrointestinal regulatory biology (23). This is because the cellular and molecular mechanisms of python intestine appear qualitatively similar to those of traditional mammalian intestinal models, but pythons' regulatory scopes are far greater and hence much easier to measure and analyze. For example, glucose transporter activity is upregulated by a factor of 41 in python anterior intestine, but only by a

factor of 2 in mouse intestine. In addition, pythons are easier to maintain than rats and mice, because they are docile, quiet, and require feedings only at intervals of 2 wk or more. They are also very tolerant of experimental interventions (such as a pH electrode passed down the esophagus into the stomach for 1 wk) and surgical interventions [such as preparation of a Thiry-Vella loop of intestine (27)].

The results of the present paper should prove useful in selecting those conditions of meal size and time after feeding that will be most advantageous for analyzing the mechanisms underlying particular regulatory responses. For instance, Fig. 6 suggests that glucose transporter upregulation and aspartate transport upregulation would be best studied in both the anterior and distal small intestine, respectively, but at 3 days after feeding a large meal (e.g., 65% of snake body mass). In contrast, Fig. 4 suggests that intestinal growth would be best studied at 1 day after feeding a medium-sized meal (e.g., 25% of snake body mass), because a larger meal produces no additional growth.

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Address for reprint requests: S. M. Secor, Dept. of Physiology, UCLA School of Medicine, 10833 Le Conte Ave., Los Angeles, CA 90095–1751.

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