The Journal of Experimental Biology 211, 3767-3774
Published by The Company of Biologists 2008
doi:10.1242/jeb.023754

Commentary

Digestive physiology of the Burmese python: broad regulation of integrated performance

Stephen M. Secor
Department of Biological Sciences, The University of Alabama, Tuscaloosa, AL 35405, USA
e-mail: ssecor@biology.as.ua.edu

Accepted 10 October 2008

Summary

As an apparent adaptation to predictably long episodes of fasting, the sit-and-wait foraging Burmese python experiences unprecedented regulation of gastrointestinal and cardiovascular performance with feeding and fasting. The ingestion of a meal signals the quiescent gut tissues to start secreting digestive acid and enzymes, to upregulate intestinal brush-border enzymes and nutrient transporters, and to grow. An integrated phenomenon, digestion is also characterized by increases in the mass, and presumably the function, of the heart, pancreas, liver and kidneys. Once digestion is complete, the python's stomach and small intestine rapidly downregulate performance. Much of the modulation of intestinal function can be explained by the 5-fold increase in microvillus length and apical surface area with feeding, and the subsequent shortening of the microvilli after digestion has finished. Digestion for the Burmese python is a relatively expensive endeavor, evident by the as much as a 44-fold increase in metabolic rate and equivalent in cost to as much as 37% of the meal's energy. Their large metabolic response is supported by substantial increases in ventilation and cardiac output and the apparent catabolism of glucose and lipids. Unmatched in the magnitude of its numerous physiological responses to feeding, the Burmese python is a very attractive model for examining the capacities and regulatory mechanisms of physiological performance.

Key words: cardiovascular, digestion, gastrointestinal, postprandial response, python model, *Python molurus*, regulation, specific dynamic action.

Introduction

Unlike snake species that widely forage for their prey and typically feed relatively frequently, pythons, as well as many boas, vipers and pit vipers, employ the sit-and-wait tactic of hunting (Greene, 1997). This foraging mode successfully balances low foraging costs with modest rates of energy intake; as such, snakes repeatedly spend weeks and even months between meals (Slip and Shine, 1988; Secor and Nagy, 1994; Wilson, 2007). For the Burmese python, native to southeastern Asia, the next meal could range from a monitor lizard or ground-dwelling bird to a prey as formidable as a pangolin, deer or leopard (Wall, 1912; Murphy and Henderson, 1997). When it does eventually capture a prey and feed, the python's previously dormant gut rapidly resumes function to tackle the difficult task of digesting a prey that may exceed half of the python's own body mass. Once digestion is complete, the python's gut and associated organs return to their previous quiescent state, where they remain until the next meal.

For the past 15 years, the Burmese python as well as other species of sit-and-wait foraging snakes (rattlesnakes, boas and other pythons) have been the subject of physiological study, especially of their digestive and cardiovascular systems (Secor et al., 1994; Secor and Diamond, 1995; Overgaard et al., 1999; Secor et al., 2000b; Andrade et al., 2004; Starck and Wimmer, 2005; Ott and Secor, 2007). The attention that Burmese pythons and these other snakes have received stems from the unprecedented magnitude of their morphological and physiological responses to feeding and fasting. This trait potentially allows the many mechanisms underlying digestive responses to be easily studied and identified (Secor and Diamond, 1998). The attractiveness of the Burmese python as a research model is also aided by the ease of procurement through the commercial animal trade, and the fact that they are generally very docile and easy to maintain, and are amenable to a variety of different experimental treatments.

The aim of this Commentary is to provide an updated and comprehensive narrative of the digestive responses of the Burmese python. The findings described originate from studies that used pythons raised in captivity (usually 400–1000 g) that were fed a rodent meal weighing approximately 20–25% of the snake's body mass. While much of the information presented originates from published articles, I have also included findings recently presented at scientific meetings. In covering the responses of different tissues, I shall illustrate the integrated nature of the Burmese python's feeding and fasting responses.

The ups and downs of python digestion

While the Burmese python lies in wait for its next meal, its gastrointestinal (GI) tract is quiescent, having been downregulated in structure and function following the digestion of its previous meal. In this state the stomach does not produce acid, secretion from the gall bladder and pancreas has ceased, the activity of intestinal nutrient transporters and enzymes is depressed, the intestinal epithelium is in an atrophied state and the intestinal microvilli are short stubs not more than half a micrometer in length (Secor and Diamond, 1995; Starck and Beese, 2001; Secor, 2003; Lignot et al., 2005; Cox and Secor, 2008). The activity of other organs is also reduced and is associated with a reduction in the mass of the heart, liver, pancreas and kidneys, and a suppressed cardiac

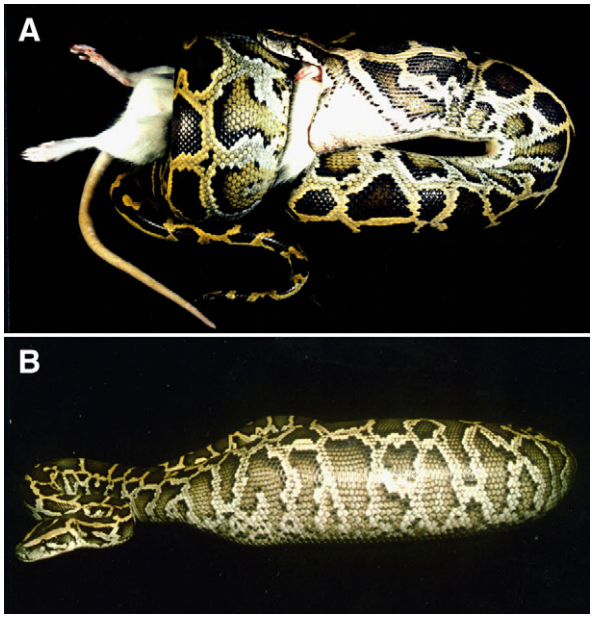

Fig. 1. (A) A Burmese python swallowing a laboratory rat which it had killed by constriction. (B) A Burmese python 24 h after consuming a rat meal greater than 50% of the snake's body mass. This snake had experienced further distension of its body after feeding due to the build up of gases within the ingested dead rat.

output (Secor and Diamond, 1995; Starck and Beese, 2001; Secor et al., 2000b; Cox and Secor, 2008).

When a prey item passes by, the python lunges with its mouth wide open, impaling the prey with its teeth before coiling itself around the victim (Fig. 1A). For the prey, death comes by constriction as the coils tighten and compress the thoracic cavity, preventing ventilation and impeding cardiac output and blood flow to and from the head. Once the prey is dead the python begins swallowing it, usually head first, using its paired set of pterygoid teeth in alternating fashion to literally walk its skull over the prey. Possessing a skull with an extreme amount of mobility, an elastic ligament between the lower jaws and a multi-hinged jaw joint, pythons are able to consume prey items that are several times wider than their own head. Swallowing of their prey, especially of large items, is aided by contractions of axial muscles that drive the prey through the expandable esophagus and into the stomach. Although the cost of constriction and swallowing has not been examined for Burmese pythons, we can surmise from an elegant study on boa constrictors that these actions significantly increase metabolic rate and are equivalent in cost to approximately 0.1–0.2% of the meal's energy (Canjani et al., 2003).

Once the prey is within the snake's stomach, the real challenge begins, for the dead intact prey begins to putrefy. Gas produced by the prey's resident bacteria distends the prey, further expanding the snake's girth (Fig. 1B). While it is inconceivable that the snake's stomach and body wall would rupture from this pressure, the compression that the expanded stomach and lower esophagus exert on the lungs and vascularization may interfere with ventilation and blood flow. Therefore it is necessary for the python to rapidly initiate breakdown of the prey to both relieve this pressure and move the meal into the small intestine. However, in the absence of a steady baseline rate of fasting acid production, which is characteristic of mammals, the oxyntopeptic cells of the python's

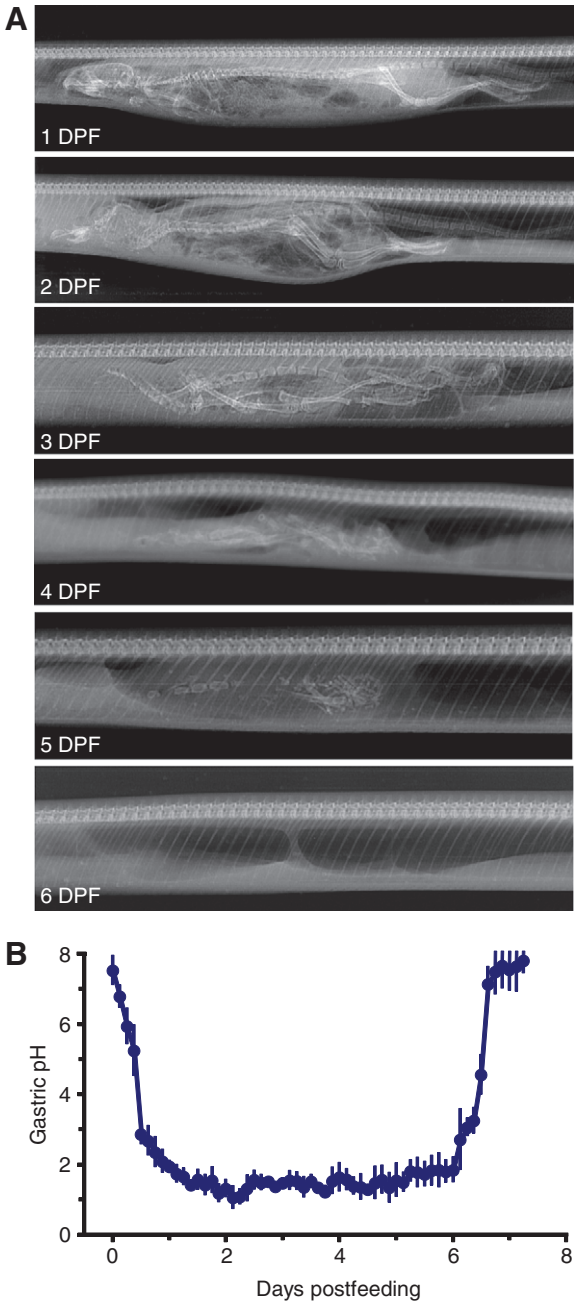

Fig. 2. (A) Daily X-ray images of a python digesting a rat that was equal to 25% of the snake's body mass. At 1 day postfeeding (DPF), the rat's skeleton is completely intact within the python's stomach, whereas by day 6 the rat's skeleton has been completely broken down and passed into the small intestine. (B) The postprandial profile of gastric pH for Burmese pythons demonstrating the rapid drop in pH after feeding, the steady maintenance of a very acidic pH during digestion, and the rise in pH upon the completion of gastric digestion when acid production ceases. Error bars in B and subsequent figures represent ±1 s.e.m. Gastric pH profile redrawn from data presented in Secor (Secor, 2003).

gastric mucosa must rapidly begin pumping H^+ while releasing the inactive protease pepsinogen and Cl^- into the lumen of the gastric pits (Forte et al., 1980).

HCl production drops luminal pH from 7 to 2 within 24 h and this together with the cleaved pepsinogen product, pepsin, causes the soft tissues and skeleton of the prey to begin to dissolve, starting

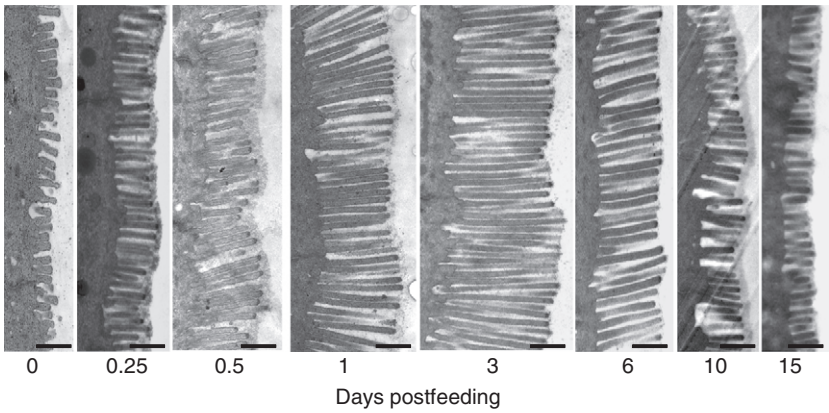

Fig. 3. Transmission electron micrographs illustrating the rapid postprandial lengthening of the python's intestinal microvilli, reaching a peak in length at 3 days postfeeding. After digestion is complete (after day 6), the microvilli shorten in length. Bar in images represent 1 μm.

at the head (Secor, 2003) (Fig. 2). Pythons continue HCl production at a rate that maintains a luminal pH of 1.5–2 in spite of the large buffering capacity of the meal itself (Fig. 2). To fuel the H^+/K^+-ATPase (proton pumps), the python's oxyntopeptic cells are packed with mitochondria (40–50% by volume). By day 3 of digestion, only 25% of the ingested meal remains within the stomach, and it is largely composed of portions of trunk vertebrae, hind limbs, tail and hair. After 6 days, all that may remain within the stomach is a mat of hair (Cox and Secor, 2008) (Fig. 2).

The release of gastric chyme from the stomach into the small intestine is metered by alternating contractions and relaxations of the pyloric sphincter. As much as 4.3 g of chyme may pass per hour into the small intestine for a 700 g Burmese python (Secor and Diamond, 1997a). Upon entry into the small intestine, the acidic chyme is rapidly neutralized, presumably by secreted HCO_3^-, such that the chyme pH increases from 2.5 to 6.5 within several centimeters (Secor et al., 2006). The chyme is also immediately joined by bile released by the gall bladder and amylase, lipase and a slew of inactive proteases released by the pancreas. Bile release is associated with a 64% decrease in gall bladder contents after feeding, and the enzyme release is associated with the rapid postprandial appearance of zymogen granules (storage depots of active and inactive enzymes) within pancreatic acinar cells and activated trypsin within the intestinal lumen (Secor and Diamond, 1995; Cox and Secor, 2008).

Even before the chyme has entered the small intestine, this previously dormant tissue has already begun to upregulate form and function. Within 6 h of feeding, with the prey still intact within the stomach, the small intestine has responded by doubling microvillus length, amino acid uptake rates, and aminopeptidase-N activity (Secor and Diamond, 1995; Lignot et al., 2005; Cox and Secor, 2008) (Figs 3 and 4). Twenty-four hours after feeding, 17–27% of the prey has entered the small intestine, which has increased in mass by 70%, quadrupled in microvillus length, and increased nutrient uptake and hydrolase activity 3- to 10-fold (Secor and Diamond, 1995; Lignot et al., 2005; Cox and Secor, 2008). Peaks in intestinal form and function are usually observed at day 2 or 3 of digestion when as much as 75% of the prey has passed out of the stomach (Secor and Diamond, 1995; Lignot et al., 2005; Cox and Secor, 2008) (Figs 3 and 4). At this time, the small intestine has dramatically increased its synthesis of oleoylethanolamide, a lipid mediator known to induce satiety, more than 300-fold (Astarita et al., 2006).

Two days after feeding, unabsorbed material (largely hair) begins to enter the large intestine. Interestingly at this junction, the large intestine extends anteriorly to form a blind-end pouch, a cecum, and continues posteriorly to the cloaca. Among snakes, only pythons, some boas and several other primitive lineages possess a cecum, whereas for most other species the small intestine continues uninterrupted into the large intestine (Cundall et al., 1993). With each continuing day of digestion, the cecum and large intestine fill with more unabsorbed material. In addition, there is an accumulation in the distal end of the large intestine of white chalky deposits of urate that has passed from the kidneys *via* the ureters. Burmese pythons often pass a bolus of urate between 3 and 7 days after feeding, and follow this a week or two later by passing a combined bolus of urate and feces.

As the last of the meal exits the stomach and transverses the small intestine, 6 to 7 days after feeding, these organs begin to downregulate. By day 10, stomach pH has risen beyond 6, pancreatic trypsin and amylase activity have dropped by 50%, the intestine has decreased in mass by 35%, microvillus length has been reduced by 50%, and intestinal nutrient uptake rates and hydrolase activities have returned to levels not significantly different from those prior to feeding (Secor et al., 2006; Cox and Secor, 2008) (Figs 2–5). At this time, other organs have begun to reverse their postprandial response: notable is the 23% decrease in liver and kidney mass. Thus, just as pythons rapidly upregulate the structure

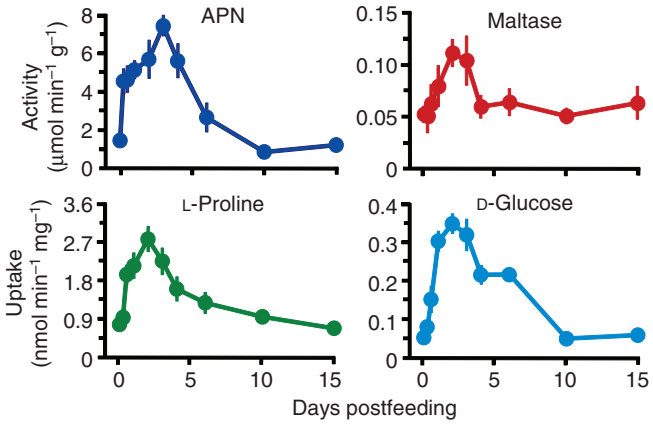

Fig. 4. Activities of the brushborder enzymes aminopeptidase-N (APN) and maltase, and uptake rates of the amino acid L-proline and the sugar D-glucose as a function of time postfeeding for the proximal region of the Burmese python's small intestine. For both proteins and simple sugars, pythons experience matched regulation of intestinal digestion and absorption. Enzyme activity profiles taken from Cox and Secor (Cox and Secor, 2008).

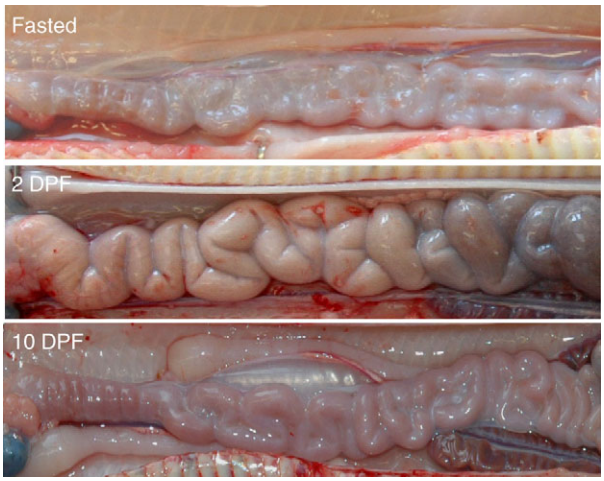

Fig. 5. Images of the small intestine of similar-sized Burmese pythons fasted and at 2 and 10 days postfeeding (DPF). By 2 DPF, the intestine has increased in diameter due primarily to hypertrophy of the epithelial cells; a response that has reversed by 10 DPF.

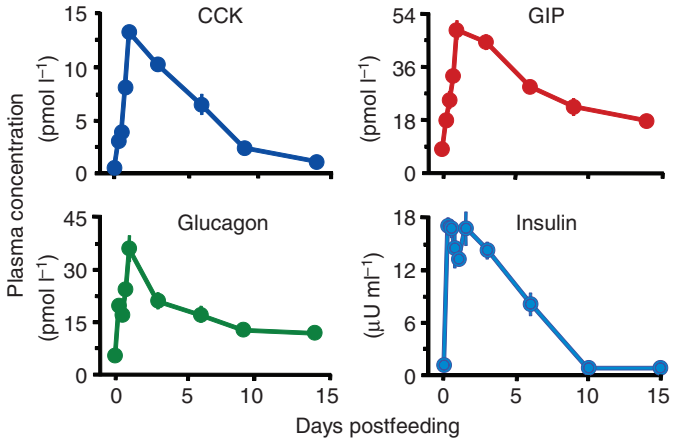

Fig. 6. Plasma concentrations of cholecystokinin (CCK), glucose-dependent insulinotropic peptide (GIP), glucagon and insulin as a function of time postfeeding for the Burmese python. The dramatic postprandial release into circulation of these regulatory peptides may serve to signal the upregulation of tissue structure and function. Profiles of CCK, GIP and glucagon redrawn from data presented in Secor et al. (Secor et al., 2001).

and function of tissues and organs after feeding begins, so they downregulate tissue mass and performance at a similar pace with the final passage of the meal.

Mechanisms of regulation

So how does the Burmese python rapidly modulate gut form and function with each meal? Two proximate pathways, hormonal and luminal, appear to signal the regulation of GI morphology and activity. Evidence for a hormonal role includes the rapid postprandial increase (as much as 25-fold) in plasma concentration of several GI peptides, including cholecystokinin, neurotensin, glucagon, insulin and glucose-dependent insulinotropic peptide (Fig. 6). At the same time as their plasma levels are increasing, the concentrations of these peptides decline within their tissues of origin (Secor et al., 2001). Another piece of evidence for a hormonal role is the observation that intestinal segments isolated from contact with luminal nutrients, but still maintaining a vascular supply, can with time upregulate function after feeding (Secor et al., 2000a). The importance of a luminal signal in triggering the initial intestinal response was identified from the direct infusion of different nutrient solutions into the python's small intestine. In response to the direct infusion of a mixed amino acid or protein solution, the small intestine upregulates function and experiences hypertrophy of the epithelium (Secor et al., 2002). In contrast, the infusion of a saline, glucose or lipid solution into the small intestine does not elicit any increase in function (Secor et al., 2002).

The observed increase in the mass of the small intestine primarily originates from hypertrophy (growth) of the epithelial cells (enterocytes), and is secondarily due to hyperplasia (cellular replication). Enterocytes increase in width by 40% after feeding, resulting in lengthening of the villi and thickening of the mucosa (Lignot et al., 2005). For enterocytes that populate the tips and edges of the villi in the anterior small intestine, their increase in width is contributed in part by the absorption of lipids originating from the meal (Starck and Beese, 2001; Lignot et al., 2005). A postprandial increase in the rate of enterocyte replication has been observed for Burmese pythons using several different techniques (Secor et al., 2000a; Starck and Beese, 2001; Lignot and Secor, 2003). Python enterocytes continue to replicate during fasting, although after feeding rates of replication increase severalfold (Secor et al., 2000a; Starck and Beese, 2001; Lignot and Secor, 2003). The extent to which hyperplasia contributes to mucosal growth appears to be dampened by the concurrent increase in apoptosis, programmed cell death (Lignot and Secor, 2003). This suggests that the intestinal epithelium of the Burmese python experiences a postprandial increase in the rate of cell turnover, which may stem from the greater activity of the cells and their increased exposure to luminal contents.

The capacity of the python's intestine to modulate nutrient uptake and enzyme activities stems from one or several different cellular mechanisms. We could imagine that apical membrane nutrient transporters and enzymes simply increase or decrease their rates of activity, as proposed for developmental changes in intestinal function associated with ontogenetic shifts in diet (Buddington and Diamond, 1992; Toloza and Diamond, 1990). Alternatively, python enterocytes could increase the synthesis of transporters and enzymes with feeding, and increase the density of these apical proteins, thereby increasing mass-specific function. This mechanism has been used to explain the increase in glucose uptake for mice switched from a low to a high carbohydrate diet (Ferraris et al., 1992). A third mechanism would involve an increase in the apical surface area of enterocytes. Pythons actually experience such a response with the postprandial lengthening of their microvilli. By assuming that membrane transporter and enzyme densities remain unchanged, the 5-fold length change of the microvilli would generate a similar relative increase in function. In general, intestinal uptake rates and enzyme activities increase by 3- to 8-fold with feeding (Secor and Diamond, 1995; Cox and Secor, 2008). The shortening of the microvilli once digestion is complete would therefore explain the concurrent downregulation of intestinal nutrient transport and enzyme activities.

Whilst we can explain much of the regulation of intestinal function by the modulation of microvillus length, what we cannot explain at present is the means by which the microvilli lengthen and shorten so quickly. Because this response in pythons is unprecedented in the literature, there are no prior descriptions of

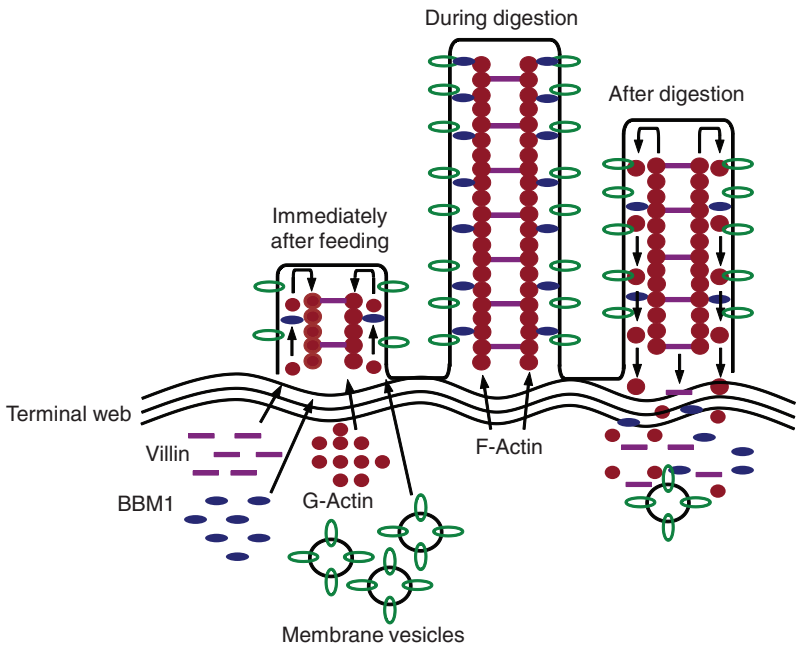

Fig. 7. Hypothetical model of the cellular mechanisms involved in the postprandial lengthening of the python's intestinal microvilli and subsequent shortening of the microvilli once digestion is complete. In this scenario, structural proteins and vesicles of membrane sequestered within the cytoplasm during fasting rapidly migrate to the apical membrane with feeding and are inserted in place to further lengthen the existing microvilli. After digestion is complete, the components of the microvilli are either released into the lumen or return back to the cytosol for reuse.

the cellular mechanisms that result in rapid lengthening of intestinal microvilli. The most parsimonious scenario is that all of the individual components of the microvilli are sequestered within the enterocyte cytoplasm and feeding triggers a signaling cascade that results in the trafficking of these components to the apical edge. There they are assembled on the tips of the pre-existing microvilli in a similar fashion to the construction of a skyscraper (Fig. 7). The polymerization of monomeric G-actin into filamentous F-actin, which forms the microvillus internal skeleton, is important in this process. Evidence for this process includes our observation of a shift from G-actin-laden enterocytes in fasted pythons to a dense concentration of apical F-actin after feeding. Additionally, we have found in preliminary studies that the postprandial growth of the python's microvilli is stunted by the direct administration of cytochalasin D, an inhibitor of actin polymerization, into the small intestine.

Why regulate?

It is important to note that the regulation of GI function and morphology is not a novel phenomenon found in pythons alone but, rather, is practiced (to some extent) by all vertebrates. The modulation of GI activities and structure in response to changes in digestive demand has been well recorded for a wide diversity of vertebrates (Hammond and Diamond, 1994; Secor and Diamond, 2000; McWilliams and Karasov, 2001; Kroghdahl and Bakke-Mckellep, 2005; Secor, 2005a). What sets pythons, and other infrequently feeding snakes, apart is the sheer magnitude of their regulatory response. Instead of a 25–50% increase in intestinal mass and a 50–100% increase in mass-specific nutrient uptake rates commonly observed with feeding or a change in diet, pythons double the mass of their small intestine and increase nutrient uptake rates by 5- to 10-fold (Secor, 2005b; Ott and Secor, 2007). When integrated for the complete small intestine, the capacity to hydrolyze and absorb nutrients with an increase in demand may at best double for most vertebrates. For the python, however, intestine functional capacity increases as much as 10- to 20-fold after feeding, before declining after digestion is completed (Secor, 2005b; Ott and Secor, 2007).

Inquiries into why pythons regulate GI performance so dramatically have focused our attention on the postdigestive downregulatory responses rather than on the impressive postfeeding upregulatory responses. Any organism that is predestined to feed infrequently due to their particular feeding habits or strict seasonality of food would benefit from the selection for a reduced rate of basal energy expenditure. Of all the tissues of the body, those of the gut are relatively expensive to maintain due in part to the costs of acid production, pancreatic and intestinal secretion, nutrient transport, ion homeostasis and epithelial turnover (Reenstra and Forte, 1981; Cant et al., 1996; Nyachoti et al., 2000). Hence, selection would favor the depression of GI activity during long periods of fasting, especially if these periods are predictable. Although the energy expended by an idling snake gut has not been quantified, we have found that species of snakes that downregulate their guts with fasting possess standard metabolic rates that are almost 50% lower than rates characteristic of snakes species that feed more frequently and only modestly regulate their guts with fasting (Secor and Diamond, 2000; Ott and Secor, 2007). The downregulation of GI form and function by pythons and other infrequently feeding snakes after completing digestion can therefore be envisaged as an adaptive response that serves to conserve energy during predictable long episodes of fasting (Secor and Diamond, 2000b; Secor, 2005b). On the other side of the coin, the preferred adaptive strategy for frequently feeding snakes is to maintain an idling intestinal tract during their short bouts of fasting (Secor and Diamond, 2000; Secor, 2005b). Testing the validity of these adaptive scenarios for snakes, other reptiles and even amphibians will require further examination of the fasting and feeding responses of the GI tract over a broader range of lineages and feeding habits.

An integrated effort

After feeding, the python's large intact meal stimulates, for as much as a week, the continuous production of gastric HCl and pepsin and pancreatic enzymes, the constant activity of intestinal brush-border enzymes, the repeated maintenance and turnover of the epithelium,

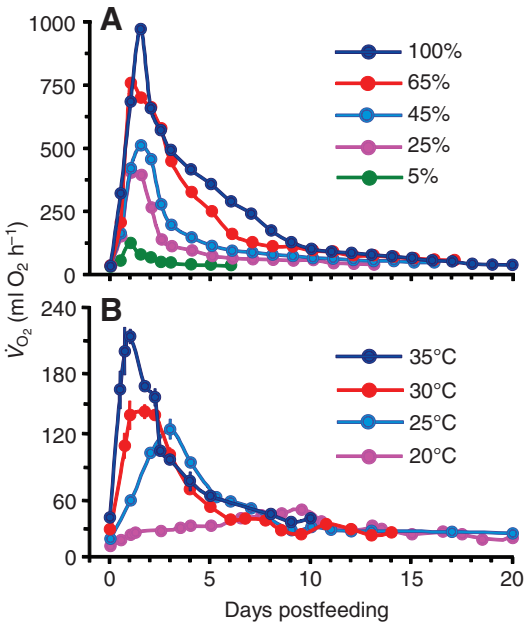

Fig. 8 The effects of meal size (% of snake body mass, A) and body temperature (B) on the postprandial profile of $\dot{V}_{O_2}$ (ml h^{-1}) for juvenile Burmese pythons. Increasing meal size generates a more elevated and prolonged metabolic response. With an increase in body temperature, the metabolic profile becomes narrower and higher. A and B redrawn from data presented in Secor and Diamond, and Wang et al., respectively (Secor and Diamond, 1997b; Wang et al., 2003).

and the non-stop transport and assimilation of generous quantities of nutrients. Python digestion consequently entails both a substantial metabolic investment and the coordinated interactions of other tissues. The accumulated energy expended on all postprandial activities involved in the digestion and assimilation of the meal is commonly referred to as specific dynamic action or SDA (Jobling, 1994). For the Burmese python, the profile of the SDA response is quite similar to that of other animals, being characterized by a rapid postfeeding increase in metabolic rate followed by a slower return to basal rates (Secor, 2009). Although similar in profile, it is the magnitude of the python's postprandial metabolic response that is eye-catching, highlighted by as much as a 44-fold increase in metabolic rate and equal to as much as 37% of the ingested meal's energy (Secor and Diamond, 1997b) (Fig. 8). Assumed to be entirely aerobic (plasma lactate <0.5 mmol l^{-1}), the python postprandial metabolic response can be significantly affected by body temperature, meal composition and size (Overgaard et al., 1999). Decreasing body temperature prolongs the metabolic response while increasing the protein content or the size of the meal generates a larger SDA response (Secor and Diamond, 1997b; Wang et al., 2003; McCue et al., 2005) (Fig. 8).

One by-product of this metabolic response is the release of heat, which increases the snake's core and surface temperatures by as much as 4 and 2.5°C, respectively (Marcellini and Peters, 1982; Powolny et al., 2007). Endogenous as well as ingested lipids and glucose are suspected to fuel the elevated tissue performance as suggested by the postfeeding increase in plasma levels and, specifically for glucose, the increased concentration of injected 2-[^{18}F]fluoro-2-deoxyglucose within tissues observed using positron emission tomography (Secor and Diamond, 1997b; Secor and Diamond, 1998; Starck et al., 2004) (Fig. 9).

The Burmese python coordinates feeding and fasting responses across organs and tissues and this is reflected in the collective changes in their mass and function. With feeding, the pancreas doubles in mass and experiences significant increases in enzyme activities, while the gall bladder declines in mass as bile is secreted into the small intestine (Secor and Diamond, 1995; Cox and Secor, 2008) (Fig. 10). The python's liver and kidneys can double in mass after feeding, which suggests matched upregulation of hepatic and renal performance in response to feeding (Secor and Diamond, 1995; Starck and Beese, 2001) (Fig. 10). Driven by the increase in tissue metabolism, the python responds with a 5-fold increase in ventilation and cardiac output, the latter being a function of a 3- to 4-fold increase in heart rate and a 50% increase in stroke volume (Secor et al., 2000b; Secor and White, 2007). The increase in stroke volume is due in part to a 40% increase in cardiac mass (Secor and Diamond, 1995; Andersen et al., 2005) (Fig. 10). As predicted, pythons experience a very large postprandial increase in intestinal blood flow, highlighted by an 11-fold increase in flow through the superior mesenteric artery (Secor and White, 2007). The Burmese python's postprandial intestinal hyperemia appears in part to be mediated (*via* vasodilatation) by the regulatory peptide neurotensin, whose plasma concentration increases 3.3-fold with feeding (Secor et al., 2001; Skovgaard et al., 2007).

Interestingly, the Burmese python's postprandial increase in ventilation does not match the increase in gas exchange, and hence they hypoventilate during digestion (Overgaard et al., 1999; Secor et al., 2000). Whilst they do not experience any postprandial change in arterial P_{O_2}, arterial P_{CO_2} does increase by approximately 30% (Overgaard et al., 1999; Overgaard and Wang, 2002). Digestion also generates an increase (35%) in plasma [HCO_3^-] and a decrease (13%) in plasma [Cl^-] due to the exchange between the circulation and the gastric epithelium of Cl^- for HCO_3^-; the former is channeled into HCl production (Secor and Diamond, 1997a; Overgaard et al., 1999; Overgaard and Wang, 2002). The potential for a postprandial metabolic alkalosis, an 'alkaline tide', resulting from increased blood [HCO_3^-] is lessened by the concurrent increase in P_{CO_2}, such that there is no significant change in arterial pH (7.45–7.62) with feeding (Overgaard et al., 1999; Overgaard and Wang, 2002).

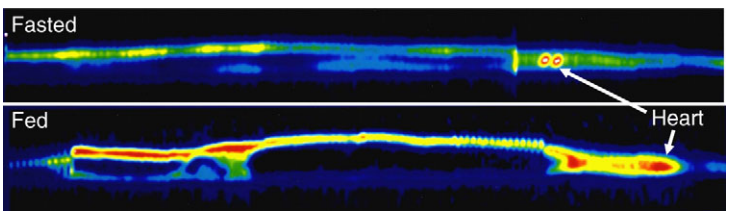

Fig. 9. Positron emission tomography (PET) images of a fasted and fed (1 day postfeeding) Burmese python. Snakes were injected with 2-[^{18}F]fluoro-2-deoxyglucose prior to scanning. Bright areas signify regions experiencing high rates of glucose metabolism. The difference between the two images is actually greater given that the intensity of the fasted image had to be increased 1000-fold in order to view the entire snake.

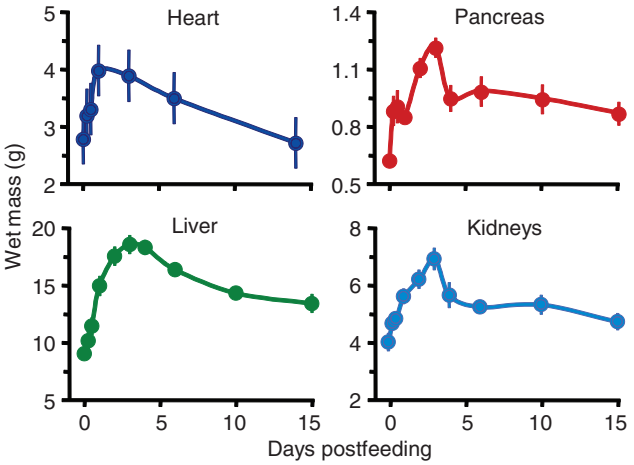

Fig. 10. Wet mass of the heart, pancreas, liver and kidneys plotted against time postfeeding for Burmese pythons fasted (0) and following the consumption of rodent meals equal to 25% of the snake's body mass. Feeding generates respective increases in wet mass of 40%, 94%, 106% and 72% for the heart, pancreas, liver and kidneys.

Insights into the python model

"*When we summon a physician to the house or consult him at his office, we do not stop to realize that many a lowly animal, such as the snake, has indirectly contributed its small share to the learning possessed by the physician*."
Francis Benedict (Benedict, 1932a)

Burmese pythons, and other sit-and-wait foraging snakes, possess a tremendous capacity to alter GI form and function with feeding and fasting (Secor and Diamond, 2000; Ott and Secor, 2007). Each meal triggers dramatic increases in metabolism, upregulation of tissue function and tissue growth. Upon the completion of digestion, these postprandial responses are thrown into reverse; tissue function is collectively downregulated and tissues undergo atrophy. The extreme plasticity of their GI tissue enables pythons to be very tractable research models to experimentally investigate the signaling and cellular mechanisms that underlie the regulation of digestive tissues (Secor and Diamond, 1998; Secor, 2005). In 1929, August Krogh wrote, 'For such a large number of problems there will be some animal of choice or a few such animals on which it can be most conveniently studied' (Krogh, 1929). Krogh was probably not thinking of the python when he penned his renowned Krogh Principle, though it is certain that the python exemplifies his sentiments. It was not that much later that the python was introduced in print as a valuable animal for research and training by Francis Benedict, the author of the quote that begins this section and the first to document the python's large postprandial metabolic response (Benedict, 1932a; Benedict, 1932b).

The feeding and fasting responses of pythons and other infrequently feeding animals will continue to attract study. Although much has been discovered regarding python digestion in the past 15 years, we have only scratched the surface in identifying the many different responses and their mechanisms. While there are many intriguing physiological phenomena of the python that still await study, a short list of candidate studies could focus on: (1) the cellular mechanisms responsible for the rapid postprandial lengthening of python intestinal microvilli and subsequent shortening after digestion; (2) the steps involved in turning on and off gastric HCl production with feeding and fasting; (3) the postprandial presence of particles of calcium phosphate within the intestinal lumen and their apparent association with specialized epithelial cells (Lignot et al., 2005; Pope et al., 2007) (Fig. 11); (4) the fate of the intestinal microbial community during long episodes of fasting and their role during digestion; and (5) the signals and mechanisms that underlie the postprandial hypertrophy of python heart, liver, pancreas and kidneys (Secor and Diamond, 1995; Starck and Beese, 2001; Andersen et al., 2005). In securing their place as a model of the Krogh Principle, pythons will continue to generate new discoveries in physiology.

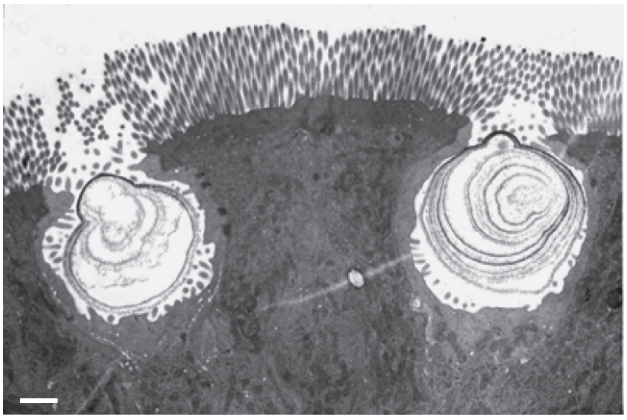

Fig. 11. Transmission electron micrograph of python intestinal epithelium embedded with spherical particles composed of calcium and phosphate. It is hypothesized that the source of the calcium and phosphate is the degraded skeleton of the rodent meal (Lignot et al., 2005). The bar in the image represents 1 μm.

My sincerest appreciation is extended to my colleagues, graduate students and undergraduates who have joined me in the exploration of python physiology. I must thank Jared Diamond who in asking me whether infrequently feeding snakes possess unique features of their digestive system provided the initial spark and support for this research program. I am grateful to Jean-Hervé Lignot, friend and colleague, who also recognized the uniqueness of the python gut and has joined me in studying its structural plasticity. Support for my research on pythons has been provided by National Institutes of Health (GM 14772 and DK 42973), National Science Foundation (IOS 0466139) and The University of Alabama.

References

Andersen, J. B., Rourke, B., Caiozzo, V., Bennett, A. F. and Hicks, J. W. (2005). Postprandial cardiac hypertrophy in pythons. *Nature* **434**, 37-38.
Andrade, D. V., De Toledo, L. P., Abe, A. S. and Wang, T. (2004). Ventilatory compensation of the alkaline tide during digestion in the snake *Boa constrictor*. *J. Exp. Biol.* **207**, 1379-1385.
Astarita, G., Rourke, B. C., Andersen, J. B., Fu, J., Kim, J. H., Bennett, A. F., Hicks, J. W. and Piomelli, D. (2006). Postprandial increase of oleoylethanolamide mobilization in small intestine of the Burmese python (*Python molurus*). *Am. J. Physiol.* **290**, R1407-R1412.
Benedict, F. G. (1932a). Reptiles used in study of human physiology. *Carnegie Institution of Washington, News Service Bulletin* **2**, 193-197.
Benedict, F. G. (1932b). *The Physiology of Large Reptiles with Special Reference to the Heat Production of Snakes, Tortoises, Lizards and Alligators*. Washington: Carnegie Institution.
Buddington, R. K. and Diamond, J. (1992). Ontogenetic development of nutrient transporters in cat intestine. *Am. J. Physiol.* **263**, G605-G616.
Canjani, C., Andrade, D. V., Cruz-Neto, A. P. and Abe, A. S. (2003). Aerobic metabolism during predation by a boid snake. *Comp. Biochem. Physiol.* **133A**, 487-498.
Cant, J. P., McBride, B. W. and Croom, W. J. (1996). The regulation of intestinal metabolism and its impact on whole animal energetics. *J. Anim. Sci.* **74**, 2541-2553.
Cox, C. L. and Secor, S. M. (2008). Matched regulation of gastrointestinal performance for the Burmese python, *Python molurus*. *J. Exp. Biol.* **211**, 1131-1140.
Cundall, D., Wallach, V. and Rossman, D. A. (1993). The systematic relationship of the snake genus *Anomochilus*. *Zool. J. Linn. Soc.* **109**, 275-299.
Ferraris, R. P., Villenas, S. A., Hirayama, B. A. and Diamond, J. M. (1992). Effect of diet on glucose transporter density along the intestinal crypt/villus axis. *Am. J. Physiol.* **262**, G1060-G1068.

Forte, J. G., Machen, T. E. and Öbring, K. J. (1980). Mechanisms of gastric H^+ and Cl^- transport. *Annu. Rev. Physiol.* **42**, 111-126.
Greene, H. W. (1997). *Snakes: The Evolution of Mystery in Nature*. Berkley: University of California Press.
Hammond, K. A. and Diamond, J. (1994). Limits to nutrient intake and intestinal nutrient uptake capacity during extended lactation. *Physiol. Zool.* **67**, 282-303.
Jobling, M. (1994). *Fish bioenergetics*. London: Chapman & Hall.
Krogdahl, Å. and Bakke-Mckellep, A. M. (2005). Fasting and refeeding cause rapid changes in intestinal tissue mass and digestive enzyme capacities in Atlantic salmon (*Salmo salar* L.). *Comp. Biochem. Physiol.* **141A**, 450-460.
Krogh, A. (1929). Progress of physiology. *Am. J. Physiol.* **90**, 243-251.
Lignot, J. H. and Secor, S. M. (2003). Apoptosis in the intestinal mucosa of the Burmese python. *Integr. Comp. Biol.* **43**, 878.
Lignot, J. H., Helmstetter, C. and Secor, S. M. (2005). Postprandial morphological response of the intestinal epithelium of the Burmese python (*Python molurus*). *Comp. Biochem. Physiol.* **141A**, 280-291.
Marcellini, D. L. and Peters, A. (1982). Preliminary observations on endogenous heat production after feeding in *Python molurus*. *J. Herpetol.* **16**, 92-95.
McCue, M. D., Bennett, A. F. and Hicks, J. W. (2005). The effect of meal composition on specific dynamic action in Burmese pythons (*Python molurus*). *Physiol. Biochem. Zool.* **78**, 182-192.
McWilliams, S. R. and Karasov, W. H. (2001). Phenotypic flexibility in digestive system structure and function in migratory birds and its ecological significance. *Comp. Biochem. Physiol.* **128A**, 579-593.
Murphy, J. C. and Henderson, R. W. (1997). *Tales of Giant Snakes: A Historical Natural History of Anacondas and Pythons*. Malabar, FL: Krieger Publishing.
Nyachoti, C. M., de Lange, C. F. M., McBride, B. W., Leeson, S. and Schulze, H. (2000). Dietary influence on organ size and *in vitro* oxygen consumption by visceral organs of growing pigs. *Livest. Prod. Sci.* **65**, 229-237.
Ott, B. D. and Secor, S. M. (2007). Adaptive regulation of digestive performance in the genus *Python*. *J. Exp. Biol.* **210**, 340-356.
Overgaard, J. and Wang, T. (2002). Increased blood oxygen affinity during digestion in the snake Python molurus. *J. Exp. Biol.* **205**, 3327-3334.
Overgaard, J., Busk, M., Hicks, J. W., Jensen, F. B. and Wang, T. (1999). Respiratory consequences of feeding in the snake *Python molorus*. *Comp. Biochem. Physiol.* **124A**, 359-365.
Pope, R., Helmstetter, C., Lignot, J. H. and Secor, S. (2007). Bone absorption through specialised intestinal cells in juvenile Burmese pythons. *Comp. Biochem Physiol.* **146A**, S174.
Powolny, T., Helmstetter, C., Pope, R. K., Reix, N., T'Flachebba, M., Secor, S. M. and Lignot, J. H. (2007). Thermogenesis of digestion in juvenile Burmese pythons. *Integr. Comp. Biol.* **47**, e220.
Reenstra, W. W. and Forte, J. G. (1981). H^+/ATP stoichiometry for the gastric (K^++ H^+)-ATPase. *J. Membr. Biol.* **61**, 55-60.
Secor, S. M. (2003). Gastric function and its contribution to the postprandial metabolic response of the Burmese python *Python molurus*. *J. Exp. Biol.* **206**, 1621-1630.
Secor, S. M. (2005a). Physiological responses to feeding, fasting, and estivation for anurans. *J. Exp. Biol.* **208**, 2595-2608.
Secor, S. M. (2005b). Evolutionary and cellular mechanisms regulating intestinal performance of amphibians and reptiles. *Integr. Comp. Biol.* **45**, 66-78.
Secor, S. M. (2009). Specific dynamic action: a review of the postprandial metabolic response. *J. Comp. Physiol. B* (in press).
Secor, S. M. and Diamond, J. (1995). Adaptive responses to feeding in Burmese pythons: pay before pumping. *J. Exp. Biol.* **198**, 1313-1325.
Secor, S. M. and Diamond, J. (1997a). Effects of meal size on postprandial responses in juvenile Burmese pythons (*Python molurus*). *Am. J. Physiol.* **272**, R902-R912.
Secor, S. M. and Diamond, J. (1997b). Determinants of the postfeeding metabolic response in Burmese pythons (*Python molurus*). *Physiol. Zool.* **70**, 202-212.
Secor, S. M. and Diamond, J. (1998). A vertebrate model of extreme physiological regulation. *Nature* **395**, 659-662.
Secor, S. M. and Diamond, J. (2000). Evolution of regulatory responses to feeding in snakes. *Physiol. Biochem. Zool.* **73**, 123-141.
Secor, S. M. and Nagy, K. A. (1994). Energetic correlates of foraging mode for the snakes *Crotalus cerastes* and *Masticophis flagellum*. *Ecology* **75**, 1600-1614.
Secor, S. M. and White, S. E. (2007). Cardiovascular response to digestion and exercise in the Burmese python. *Integr. Comp. Biol.* **46**, e247.
Secor, S. M., Stein, E. D. and Diamond, J. (1994). Rapid upregulation of snake intestine in response to feeding: a new model of intestinal adaptation. *Am. J. Physiol.* **266**, G695-G705.
Secor, S. M., Whang, E. E., Lane, J. S., Ashley, S. W. and Diamond, J. (2000a). Luminal and systemic signals trigger intestinal adaptation in the juvenile python. *Am. J. Physiol.* **279**, G1177-G1187.
Secor, S. M., Hicks, J. W. and Bennett, A. F. (2000b). Ventilatory and cardiovascular responses of a python (*Python molurus*) to exercise and digestion. *J. Exp. Biol.* **203**, 2447-2454.
Secor, S. M., Fehsenfeld, D., Diamond, J. and Adrian, T. E. (2001). Responses of python gastrointestinal regulatory peptides to feeding. *Proc. Natl. Acad. Sci. USA* **98**, 13637-13642.
Secor, S. M., Lane, J. S., Whang, E. E., Ashley, S. W. and Diamond, J. (2002). Luminal nutrient signals for intestinal adaptation in pythons. *Am. J. Physiol.* **283**, G1298-G1309.
Secor, S. M., Boback, S. M. and Lignot, J.-H. (2006). Spatial and temporal variation in the pH of the gastrointestinal tract of the Burmese python. *Integr. Comp. Biol.* **46**, e128.
Skovgaard, N., Conlon, J. M. and Wang, T. (2007). Evidence that neurotensin mediates postprandial intestinal hyperemia in the python, *Python regius*. *Am. J. Physiol.* **293**, R1393-R1399.
Slip, D. J. and Shine, R. (1988). Feeding habits of the diamond python, *Morelia s. spilota*: ambush predation by a boid snake. *J. Herpetol.* **22**, 323-330.
Starck, J. M. and Beese, K. (2001). Structural flexibility of the intestine of Burmese python in response to feeding. *J. Exp. Biol.* **204**, 325-335.
Starck, J. M. and Wimmer, C. (2005). Patterns of blood flow during the postprandial response in ball python, *Python regius*. *J. Exp. Biol.* **208**, 881-889.
Starck, J. M., Moser, P., Werner, R. A. and Linke, P. (2004). Pythons metabolize prey to fuel the response to feeding. *Proc. R. Soc. Lond., B, Biol. Sci.* **271**, 903-908.
Toloza, E. M. and Diamond, J. M. (1990). Ontogenetic development of nutrient transporters in bullfrog intestine. *Am. J. Physiol.* **258**, G760-G769.
Wall, F. (1912). A popular treatise on the common Indian snakes. *J. Bombay Nat. Hist. Soc.* **21**, 447-475.
Wang, T., Zaar, M., Arvedsen, S., Vedel-Smith, C. and Overgaard, J. (2003). Effects of temperature on the metabolic response to feeding in *Python molurus*. *Comp. Biochem. Physiol.* **133A**, 519-527.
Wilson, D. (2007). Foraging ecology and diet of an ambush predator: the green python (*Morelia viridis*). In *Biology of Boas and Pythons* (ed. R.W. Henderson and R. Powell), pp. 141-150. Eagle Mountain, Utah: Eagle Mountain Publishing.