The Journal of Experimental Biology 209, 1052-1057
Published by The Company of Biologists 2006
doi:10.1242/jeb.02121

Metabolic and blood gas dependence on digestive state in the Savannah monitor lizard *Varanus exanthematicus*: an assessment of the alkaline tide

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Accepted 24 January 2006

Summary

A large alkaline tide (up to 20 mmol l^{-1} increase in bicarbonate concentration [HCO_3^-] with an accompanied increase in blood pH) has previously been reported for some carnivorous reptiles within 24 h after ingesting a large meal. This phenomenon has been attributed to the secretion of large amounts of H^+ ions into the stomach, which is required for digestion of large prey items. To test the generality of this phenomenon in carnivorous reptiles, this study quantified the metabolic and acid–base status of the Savannah monitor lizard, *Varanus exanthematicus*, during digestion at 35°C. Following a meal of approximately 10% of body mass, $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ were measured continuously and arterial pH, blood gases and strong ions were measured every 8 h for 5 days. During peak digestion (24 h post feeding), $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ increased to approximately threefold fasting values ($\dot{V}_{O_2}$, 0.95–2.57 ml min^{-1} kg^{-1}; $\dot{V}_{CO_2}$ 0.53–1.63 ml min^{-1} kg^{-1}) while respiratory exchange ratio (R) remained constant (0.62–0.73). During digestion, arterial P_{CO_2} increased (from 4.6 kPa to 5.8 kPa), and [HCO_3^-] also increased (from 24.1 mmol l^{-1} to 40.3 mmol l^{-1}). In contrast to early studies on crocodilians, arterial pH in *V. exanthematicus* remained relatively stable during digestion (7.43–7.56). Strong ions contributed little to the acid–base compensation during the alkalosis. Collectively the data indicate that the metabolic alkalosis associated with H^+ secretion (as indicated by increased plasma bicarbonate) is partially compensated by a respiratory acidosis.

Key words: *Varanus exanthematicus*, feeding, specific dynamic action, arterial blood gases, alkaline tide, acid–base balance, metabolic rate, pH.

Introduction

Large carnivorous reptiles may experience an increase in oxygen consumption ($\dot{V}_{O_2}$) during digestion that is as large as that achieved during activity (Andrade et al., 1997; Hicks et al., 2000; Secor and Diamond, 1995; Secor et al., 2000). While the metabolic level reached during these two physiological challenges is similar, there are considerable temporal differences in their development. During exercise, reptiles immediately respond with an increase in metabolic rate, which then returns to resting levels shortly after cessation of exercise (Garland et al., 1987; Wagner and Gleeson, 1997; Wang et al., 1997). This pattern differs from digestive metabolic responses which take hours to develop and have an extended duration lasting days (Coulson et al., 1950a; Coulson et al., 1950b; Hicks et al., 2000; Jorgensen, 1992; Secor et al., 2000). The increased $\dot{V}_{O_2}$ associated with digestion has been attributed primarily to the preparation of the gut for digestion *via* protein synthesis and secretion of digestive compounds (Andrade et al., 1997; Secor and Diamond, 1995), including acid secretion by the stomach (Secor, 2003).

Cardiopulmonary studies during digestion in two species of reptiles (Glass et al., 1979; Hicks et al., 2000; Secor et al., 2000) found a relative hypoventilation during digestion in comparison to either rest or activity.

The postprandial response is also associated with alkalization of the blood, known as the alkaline tide. Recent studies in alligators, pythons and boas reexamined the postprandial changes in pH (Andrade et al., 2004; Busk et al., 2000b; Overgaard et al., 1999) and found a significant increase in plasma [HCO_3^-], an increase in $\dot{V}_{O_2}$ but no significant change in arterial pH. However, these reptiles rely on anaerobic metabolism to a large extent, so to test the generality of the postprandial metabolic and acid–base response in reptiles it is necessary to examine a reptile species that has a relatively high aerobic capacity. The present study investigated the acid–base response during specific dynamic action (SDA) in another large carnivorous reptile, the Savannah monitor lizard, *Varanus exanthematicus*. Savannah monitor lizards belong to a group of reptiles with activity levels higher than most other reptilian groups, and they have the capacity to

maintain relatively high rates of aerobic metabolism (Wood et al., 1978). We measured the magnitude and time course of the metabolic response, blood gases, strong ions and acid–base balance associated with the postprandial metabolic response in Savannah monitor lizards.

Materials and methods

Animals

Savannah monitor lizards (*Varanus exanthematicus* Bosc) with body mass ranging from 350 to 1200 g were obtained from a commercial animal supplier (California Zoological Supply, Santa Ana, CA, USA) and housed in large plastic containers equipped with ceramic heat lamps at one end, creating a thermal gradient between 28° and 36°C. UVB (5%)-emitting fluorescent bulbs supplied light within the containers. Lights and heat lamps were maintained on a 12 h:12 h light:dark cycle. Animals were offered unlimited adult mice or rat pups and crickets once or twice weekly prior to the experimental period. Water was available at all times. This study was approved by University of California, Irvine Institutional Animal Care and Use Committee animal protocol number 2123.

Surgery

Animals were fasted for at least 3 weeks prior to surgery and experimentation. Animals were anesthetized by exposure to isoflurane (Isoflo: Abbott Laboratories, North Chicago, IL, USA). Lizards were then artificially ventilated with 2% isoflurane via a vaporizer (Dräger, Lubeck, Germany). A femoral artery was occlusively cannulated with heparin-soaked, saline filled PE-50 or PE-60 tubing (Harvard Apparatus, Inc., Holliston, MA, USA). To reduce the risk of infection and post-surgical pain, antibiotics and analgesics were administered immediately after surgery and every second day post-surgery (Enrofloxacin; Baytril, Bayer Corporation, Shawnee Mission, KS, USA and Flunixin meglumine; Flunixamine, Fort Dodge, Madison, NJ, USA, respectively). Following surgery all animals resumed voluntary breathing and were allowed to recover for at least 18 h in an 8-l plastic box in a walk-in environmental chamber set at 35°C.

Protocol

Fasting animals were placed in an 8-l metabolic chamber fashioned from a Rubbermaid box, which was placed in a temperature-controlled room at 35°C (preferred body temperature of this species) (Hicks and Wood, 1985). Room air was pulled serially through the metabolic chamber, a Drierite (anhydrous calcium sulfate; Xenia, OH, USA) column to remove water vapor, a flow meter, and oxygen and carbon dioxide gas analyzers (model S3A, Applied Electrochemistry, Inc., Sunnyvale, CA, USA and model LB2, Beckman, Schiller Park, IL, USA) at an average flow rate of 240±2 ml min^{-1} with a vacuum pump. Oxygen consumption ($\dot{V}_{O_2}$) and carbon dioxide excretion ($\dot{V}_{CO_2}$) were monitored using AcqKnowledge data acquisition software (Biopac Systems, Inc. Goleta, CA, USA) and converted to STPD. A second group of lizards was used to measure arterial pH (pH_a), blood gases and strong ions. Fasting values were measured before each meal. Blood samples were taken every 8 h post-feeding, and measurements were made using a Nova blood gas analysis system (Waltham, MA, USA). Blood gases and pH values were corrected for temperature using correction curves that were generated for *V. exanthematicus* blood as follows. Blood from *V. exanthematicus* was equilibrated over a range of oxygen and carbon dioxide tensions. Samples of this blood were then measured both by the Nova blood gas analysis system and by a Radiometer blood gas analysis system (Copenhagen, Denmark) that was thermostatted to the animal's body temperature (35°C). The differences in values between these two measurement systems were used to correct for the temperature difference between the animal's body temperature and the temperature at which the blood sample was measured in the Nova blood gas analysis system. Plasma bicarbonate concentration ($[HCO_3^-]$) was calculated from the Henderson–Hasselbalch equation ($[HCO_3^-]=\alpha P_{CO_2}\times 10^{(pH-pK')}$) using simultaneously determined pH and P_{CO_2}; α and pK' were corrected for temperature and pH (Boutilier et al., 1984). Following the fasting period, the animals were removed from the chamber and offered 10% of their body weight in rat pups; each animal ate readily within 10 min. After feeding, the animal was returned to its chamber, and metabolic rate was measured continuously and 0.2 ml blood samples were taken every 8 h post-feeding for 5 days. After each measurement cannulae were refilled with a 100 IU ml^{-1} heparin saline solution (Elkins-Sinn, Inc., Cherry Hill, NJ, USA).

Statistical tests

Repeated measures analysis of variance (ANOVA; Dunnett Test for Multiple Comparisons *vs* Control Group) was used to analyze time course data (Graphpad Software, San Diego, CA, USA). Levels of significance were assumed with P values less than 0.05. Values are reported as means ± standard error of the mean (s.e.m.); N=6 unless otherwise noted.

Results

Metabolic response

$\dot{V}_{O_2}$ of *V. exanthematicus* increased from a fasting level of 0.95±0.19 ml min^{-1} kg^{-1} to 2.57±0.85 ml min^{-1} kg^{-1} 24 h post-feeding (Fig. 1A). This increase in $\dot{V}_{O_2}$ began within 4 h post feeding, and reached a maximum at 24 h postprandial, remaining elevated above fasting values until 114 h postprandial. Carbon dioxide excretion exhibited a similar pattern to that of oxygen consumption with $\dot{V}_{CO_2}$ increasing from a fasting level of 0.53±0.31 to 1.63±0.58 ml min^{-1} kg^{-1} 24 h postprandial, and remaining elevated until 114 h postprandial (Fig. 1B). Consequently, respiratory exchange ratio (R) did not change during the course of digestion (Fig. 1C), with a mean value of 0.62±0.21 prior to feeding and 0.73±0.18 24 h postprandial.

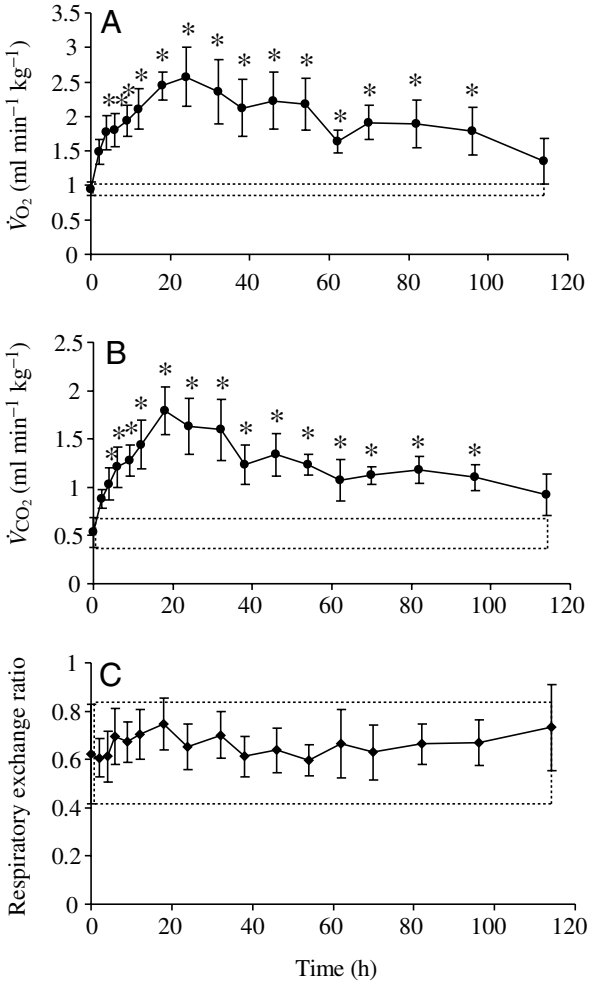

Fig. 1. Time course of postprandial (A) oxygen consumption ($\dot{V}_{O_2}$), (B) carbon dioxide secretion ($\dot{V}_{CO_2}$), and (C) respiratory exchange ratio in *Varanus exanthematicus* with time 0 representing the fasted state and all other values postprandial. Values are means ± 1 s.e.m. (N=5); asterisks mark mean values that are significantly different (P<0.05) from the fasting value. The dotted lines represent the standard error around the fasting values for comparison throughout the digestive period.

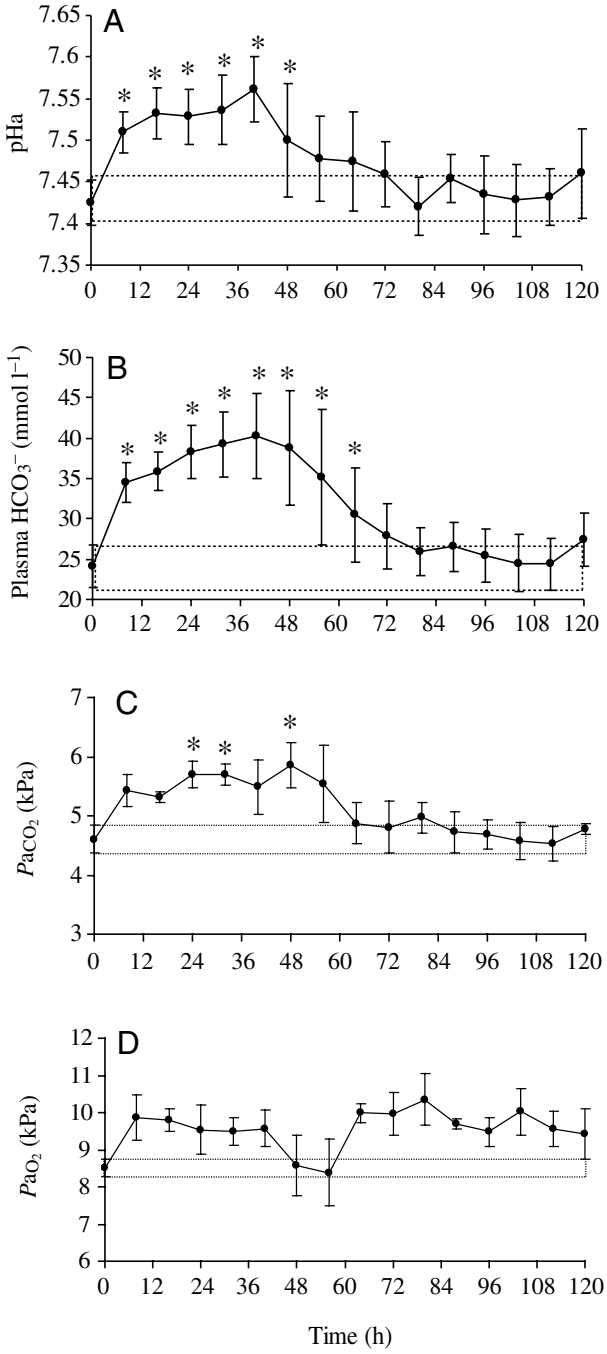

Fig. 2. Time course of postprandial change in (A) pH_a, (B) [HCO_3^-], (C) Pa_{CO_2} and (D) Pa_{O_2} in *Varanus exanthematicus* with time 0 representing the fasted state and all other values postprandial. Values are mean ± 1 s.e.m. (N=6); asterisks mark mean values that are significantly different (P<0.05) from the fasting value. The dotted lines represent the standard error around the fasting values for comparison throughout the digestive period.

Blood gases, pH and strong ions

A significant increase in pH_a was measured at 8 h after feeding (7.43±0.03 to 7.51±0.03) with an apparent peak in the alkaline tide at 40 h postprandial (7.56±0.04). pH_a was no longer significantly elevated by 56 h postprandial (Fig. 2A). Bicarbonate levels in the arterial blood increased from 24.1±2.6 mmol l^{-1} fasted to 34.6±2.4 mmol l^{-1} by 8 h postprandial with an apparent peak at 40 h postprandial (40.34±5.3 mmol l^{-1}). Bicarbonate was no longer significantly elevated by 64 h postprandial (Fig. 2B). The increase in pH_a resulting from the increase in bicarbonate was reduced by a significantly increased Pa_{CO_2} (5.7±0.2, 5.7±0.2, 5.8±0.4 kPa at 24, 32 and 48 h, respectively) compared to the fasted state (4.6±0.2 kPa; Fig. 2C). Throughout the postprandial period, Pa_{O_2} did not significantly change (Fig. 2D). Hematocrit was significantly elevated at 24 and 32 h postprandial (0.23±0.01 and 0.23±0.01, respectively) compared to the fasted state (0.2±0.01), data not shown. A significant increase in plasma lactate concentration was measured at 24 and 32 h (1.2±0.2 and

1.3±0.3 mmol l^{-1}, respectively) compared to fast (0.3±0.1 mmol l^{-1}; Fig. 3A). Chloride significantly decreased between 24 and 48 h postprandial (115.7±1.9 mmol l^{-1} at 24 h, 113.8±2 mmol l^{-1} at 32 h, 115.6±2.9 mmol l^{-1} at 40 h, 115.7±3.6 mmol l^{-1} at 48 h) compared to fast (122±1.9 mmol l^{-1}; Fig. 3B). An increase in sodium was measured at 32, 40 and 48 h postprandial (152.5±2, 150.6±1.5 and 150.7±2.4 mmol l^{-1}, respectively) compared to fast (144.7±1.7 mmol l^{-1}; Fig. 3C). Potassium levels did not change during the postprandial period (Fig. 3D).

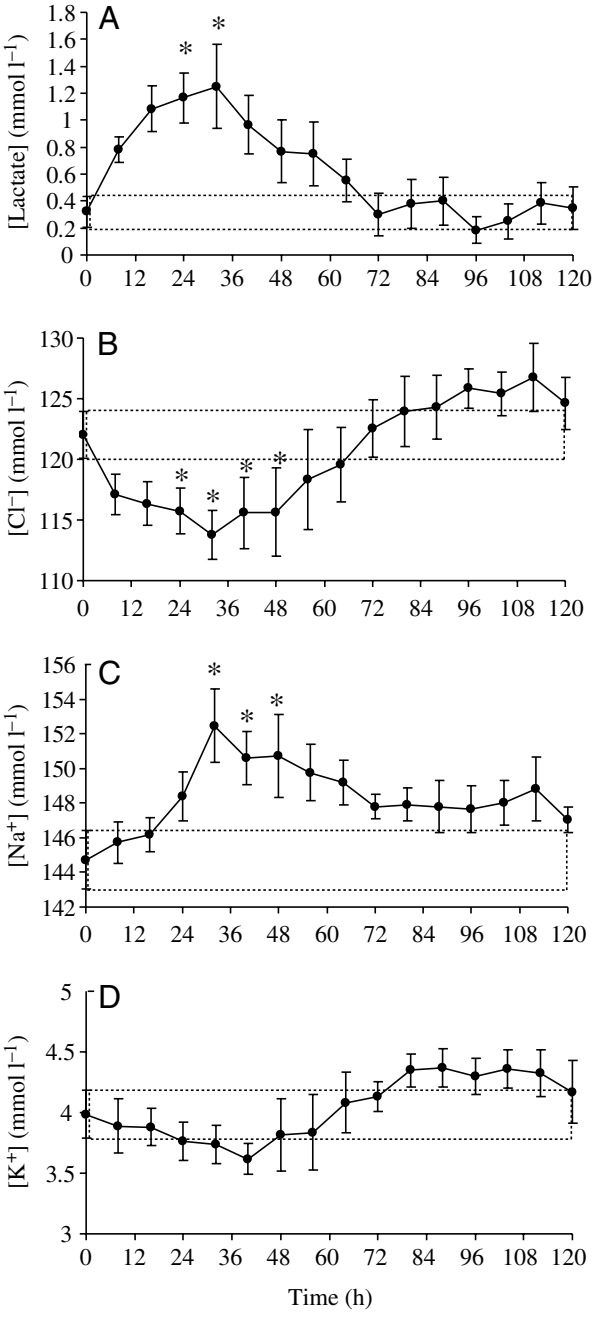

Fig. 3. Time course of postprandial change in the concentration of (A) lactate, (B) chloride, (C) sodium and (D) potassium in *Varanus exanthematicus* with time 0 representing the fasted state and all other values postprandial. Values are mean ± 1 s.e.m. (N=6); asterisks mark mean values that are significantly different (P<0.05) from the fasting value. The dotted lines represent the standard error around the fasting values for comparison throughout the digestive period.

Discussion

The postprandial metabolic response of large carnivorous reptiles typically has been reported to involve a 2- to 17-fold increase in resting $\dot{V}_{O_2}$ (Busk et al., 2000b; Hicks et al., 2000; Overgaard et al., 1999; Secor and Diamond, 1995), and the postprandial rise in $\dot{V}_{O_2}$ reported here is consistent with previous studies on *V. exanthematicus* (Fig. 1) (Hicks et al., 2000). While there was a clear metabolic elevation and an alkaline tide following feeding during this study, the alkalemia did not approach the magnitude previously reported in *Alligator mississippiensis* (Coulson et al., 1950b). The smaller increase in pH is similar to those reported in recent studies of *Python molurus* (Secor and Diamond, 1995) and *Boa constrictor* (Andrade et al., 2004), but higher than that reported for *A. mississippiensis* or *Python molurus* (Busk et al., 2000b; Overgaard et al., 1999), suggesting that the magnitude of the alkaline tide varies amongst carnivorous reptiles.

Metabolic response: fasted vs fed

Elevation in metabolic state typically accompanies digestion in vertebrates with both the increment and duration of the increase varying among species, type of forager, and relative meal size (Andrade et al., 1997; Coulson et al., 1950b; Hicks et al., 2000; Preest, 1991; Secor and Diamond, 1995; Secor and Diamond, 1997; Secor and Phillips, 1997; Secor et al., 1994; Wang et al., 1995). Reptiles are extreme with regard to metabolic changes during digestion ranging from as high as 44 times standard metabolic rate (Secor and Diamond, 1997) to this study where the increase in $\dot{V}_{O_2}$ of *V. exanthematicus* was much less (threefold increase) than that seen in *P. molurus*. As indicated by the consistency of the respiratory exchange ratio, increases in $\dot{V}_{CO_2}$ paralleled those of $\dot{V}_{O_2}$ (Fig. 1C). The time course for the postprandial metabolic response is consistent among reptiles with a peak in SDA at 24 h after feeding, lasting about 5 days (Andersen and Wang, 2003; Busk et al., 2000a; Busk et al., 2000b).

Time course of the acid-base response: fasted vs fed

In addition to the metabolic response, pH_a increased during digestion in *V. exanthematicus*; the apparent highest mean value occurred 40 h post-feeding (Fig. 2). Arterial pH peaks before metabolic rate (40 h *vs* 24 h). In *A. mississippiensis* the highest postprandial pH_a was measured at 9 h (Coulson and Hernandez, 1983). Overgaard et al. (Overgaard et al., 1999) also reported a peak in pH_a before 12 h while maximal $\dot{V}_{O_2}$ of *P. molurus* did not occur until 48 h postprandial. In this study, pH_a was significantly increased from fasting values by 8 h postprandial and remained elevated until 56 h postprandial.

Blood gas response: fasted vs fed

As illustrated in Figs 2 and 5, feeding elicits an increase in Pa_{CO_2} and [HCO_3^-], and no change in Pa_{O_2}. An increase in Pa_{CO_2} has also been reported for *A. mississippiensis* (Busk et al., 2000b), *P. molorus* (Overgaard et al., 1999), *B. constrictor* (Andrade et al., 2004), and *Bufo marinus* (Andersen and Wang, 2003). In mammals, an increase in Pa_{CO_2} is associated with a reduction in arterial Pa_{O_2}. This inverse relationship is due to the tight coupling of ventilation and metabolic rate as expressed in the alveolar ventilation equation. However, reptiles do not necessarily follow this pattern (Wang et al., 1998). Pa_{O_2} could be increased or unchanged by improving ventilation perfusion ($\dot{V}/\dot{Q}$) inhomogeneity or by decreasing the intrapulmonary or intracardiac shunt. Increase in Pa_{CO_2} could be achieved by a relative hypoventilation as has been shown in a previous study of the cardiovascular and ventilatory response to digestion in *V. exanthematicus* (Hicks et al., 2000). This hypoventilation is seen as a decrease in air convection requirement for CO_2 and probably represents changes in postprandial ventilatory control.

Strong ions

Chloride and bicarbonate exhibited the most pronounced changes after feeding, although sodium and lactate also both increased. A significant increase in lactate concentration (Fig. 3A) during the postprandial period was also seen *Scincella lateralis* (Preest, 1991), and *A. mississippiensis* (Busk et al., 2000b), but not in *Rana catesbeiana* (Busk et al., 2000a), *B. marinus* (Andersen and Wang, 2003) or *P. molorus* (Overgaard et al., 1999). Although this study measured a fourfold increase in lactate postprandially, the actual contribution of lactate to the total anion concentration is very small. The greatest changes in plasma electrolyte concentration were the decrease in chloride (secreted into the lumen of the stomach to form HCl) and the accompanying increase in bicarbonate, and, hence, the alkaline tide (Figs 2A,B, 3B). A similar decrease in chloride during the postprandial period was reported for *B. marinus* (Andersen and Wang, 2003), *R. catesbeiana* (Busk et al., 2000a) and *A. mississippiensis* (Coulson et al., 1950b). However, no change was reported in chloride concentration for *A. mississippiensis* in another study (Busk et al., 2000b), and an increase in chloride was reported for *P. molorus* (Overgaard et al., 1999).

An assessment of the alkaline tide and postprandial metabolic response

This study has delineated the changes in metabolic function as well as blood gases and acid-base status that accompany feeding in *V. exanthematicus*. There is some variation in the acid-base response to feeding in reptiles and amphibians. Some studies have reported a large increase in pH (Coulson et al., 1950b; Secor and Diamond, 1995), some a moderate increase in pH (Andrade et al., 2004; Busk et al., 2000a), and some no change in pH (Andersen et al., 2003; Andersen and Wang, 2003; Busk et al., 2000b; Overgaard et al., 1999) during the postprandial period. While it appears that there is a different response to feeding, it is rather the fasted pH values that differ most strikingly between studies. For example, fasted pH was found to be 7.36 in an early study on alligators (Coulson et al., 1950b), and 7.51 in a more recent study (Busk et al., 2000b) whereas postprandial pH in both studies was approximately 7.57; similarly, fasted pH was 7.39 in an early study on the python (Secor and Diamond, 1995), and 7.52 in a more recent study (Overgaard et al., 2002) whereas postprandial pH was 7.49 and 7.53, respectively. Each of the studies discussed above showed a significant increase in bicarbonate during the postprandial period, but the impact of the alkaline tide on the acid–base status of the animal is varied by that animal's ventilatory response (Wang et al., 2001). The response to an increase in bicarbonate post-feeding in *V. exanthematicus* is an initial metabolic alkalosis followed by a relative hypoventilation, a return to fasting pH levels, and a return to fasting Pa_{CO_2} (Fig. 4). The same response has been reported for *B. constrictor* (Andrade et al., 2004), and *B. marinus* (Andersen and Wang, 2003); however, *A. mississippiensis* showed a relative hypoventilation prior to a small metabolic alkalosis (Busk et al., 2000b).

Many of the processes involved in feeding and absorption of food contribute to the cost of digestion, and it is of interest to consider the division of cost. Secor (Secor, 2003) proposed that 55% of the metabolic cost of digestion can be attributed to the production of HCl and other gastric functions related to breakdown of the food bolus. This study measured an increase in oxygen consumption up to 5 days after feeding (Fig. 1A). Part of this cost includes the secretion of hydrogen ions into the lumen of the stomach *via* the H^+,K^+-ATPase, however, in the present study it appears that H^+ secretion does not continue past 3 days (Fig. 2). Blocking this H^+,K^+-ATPase (DiPalma, 2001) should give an estimate of the relative cost of H^+ transport. However, while omeprazole successfully blocked the alkaline tide in *B. constrictor*, the postprandial increase in

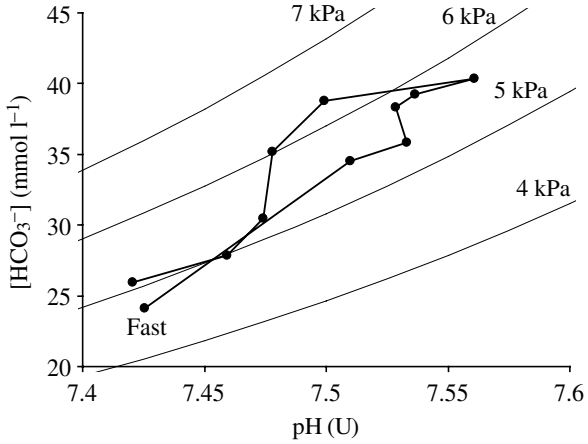

Fig. 4. Davenport diagram showing acid–base disturbance caused by feeding. Curved lines are P_{CO_2} isopleths. An initial alkalosis is followed by a relative hypoventilation (increased Pa_{CO_2}), then a return of pH to fasting levels, and, finally, a return of Pa_{CO_2} to fasting levels.

metabolic rate was indistinguishable from untreated animals (Andrade et al., 2004). This result suggests that the cost of H^+ transport is negligible in terms of the overall cost of digestion in *B. constrictor*. Other processes contributing to the cost of digestion include protein synthesis (Coulson and Hernandez, 1971; McCue et al., 2004), biosynthesis (mass) and nutrient transport (Secor and Diamond, 1995); however, the cost of increasing intestinal mass has been called into question by more recent studies (Overgaard et al., 2002; Starck and Beese, 2001; Starck and Beese, 2002) leaving the attribution of costs associated with digestion an open and interesting question.

Conclusion

It is concluded that carnivorous reptiles develop a metabolic alkalosis during digestion. Recent studies of alligators, pythons, toads and boas, as well as this study on monitor lizards, support the hypothesis that this metabolic alkalosis is partially or completely compensated by a respiratory acidosis (Andersen and Wang, 2003; Busk et al., 2000b; Coulson et al., 1950b; Hicks et al., 2000; Overgaard et al., 1999; Wang et al., 2001). The degree of compensation may explain the variability of the pH change during digestion in different species; however, why there are different degrees of compensation remains unclear.

We thank Johnnie Andersen, Amanda Szucsik, and two anonymous reviewers for comments on this manuscript; also, we thank Björn Platzack and Dane A. Crossley II for helpful advice on an earlier version of this manuscript. This paper includes a portion of the work from the dissertation of L.K.H. This research was supported by NSF grant IBN-9727762 to A.F.B. and J.W.H.

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