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Ventilatory compensation of the alkaline tide during digestion in the snake *Boa constrictor*

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Summary

The increased metabolic rate during digestion is associated with changes in arterial acid–base parameters that are caused by gastric acid secretion (the 'alkaline tide'). Net transfer of HCl to the stomach lumen causes an increase in plasma HCO_3^- levels, but arterial pH does not change because of a ventilatory compensation that counters the metabolic alkalosis. It seems, therefore, that ventilation is controlled to preserve pH and not P_{CO_2} during the postprandial period. To investigate this possibility, we determined arterial acid–base parameters and the metabolic response to digestion in the snake *Boa constrictor*, where gastric acid secretion was inhibited pharmacologically by oral administration of omeprazole.

The increase in oxygen consumption of omeprazole-treated snakes after ingestion of 30% of their own body mass was quantitatively similar to the response in untreated snakes, although the peak of the metabolic response occurred later (36 h *versus* 24 h). Untreated control animals exhibited a large increase in arterial plasma HCO_3^- concentration of approximately 12 mmol l^{-1}, but arterial pH only increased by 0.12 pH units because of a simultaneous increase in arterial P_{CO_2} by about 10 mmHg. Omeprazole virtually abolished the changes in arterial pH and plasma HCO_3^- concentration during digestion and there was no increase in arterial P_{CO_2}. The increased arterial P_{CO_2} during digestion is not caused, therefore, by the increased metabolism during digestion or a lower ventilatory responsiveness to ventilatory stimuli during a presumably relaxed state in digestion. Furthermore, the constant arterial P_{CO_2}, in the absence of an alkaline tide, of omeprazole-treated snakes strongly suggests that pH rather than P_{CO_2} normally affects chemoreceptor activity and ventilatory drive.

Key words: reptile, snake, *Boa constrictor*, feeding, postprandial period, acid–base balance, gastric acid secretion, alkaline tide, omeprazole, ventilation, ventilatory control.

Introduction

Many ectothermic vertebrates feed at irregular intervals, but are able to ingest meals that are very large relative to their own body mass (e.g. Greene, 1997; Shine et al., 1998). Digestion of these large meals is associated with considerable increments in oxygen uptake that last for several days (Benedict, 1932; Secor and Diamond, 1998; Wang et al., 2001). Digestion is also associated with changes in acid–base parameters, as gastric parietal cells are stimulated to secrete acid secretion into the stomach lumen (e.g. Hersey and Sachs, 1995; Niv and Fraser, 2002). The net transfer of HCl to the stomach leads to a reduction in plasma [Cl^-] and a concomitant increase in strong ion difference (SID; the mmolar differences between strong cations and anions; Stewart, 1983), causing plasma [HCO_3^-] concentration to increase (e.g. Wang et al., 2001; Niv and Fraser, 2002). This alkalinisation of blood and tissue is termed 'the alkaline tide' and is, at least for mammals, also accompanied by excretion of alkaline urine (Rune, 1965, 1966; Niv and Fraser, 2002). The alkaline tide is large in reptiles and amphibians (e.g. Coulson et al., 1950; Wang et al., 2001), but all species studied with indwelling catheters (to reduce stress associated with blood sampling) have shown that pHa only increases modestly because P_{aCO_2} rises during digestion (Wang et al., 1995, 2001; Overgaard et al., 1999; Busk et al., 2000a,b; Andersen and Wang, 2003). The postprandial period is characterised, therefore, by a metabolic alkalosis that is almost fully compensated by an increased P_{CO_2} that appears to be caused by hypoventilation, as ventilation does not increase proportionally to CO_2 production (Glass et al., 1979; Hicks et al., 2000; Secor et al., 2000; Wang et al., 2001). Smaller but qualitatively similar respiratory compensations have also been observed in mammals (Higgins, 1914; Erdt, 1915; Van Slyke et al., 1917; Ou and Tenney, 1974).

While it seems plausible that the respiratory compensation of pH during the postprandial period serves a homeostatic function by preventing disturbances of acid–base balance to protect enzyme function and metabolic processes, the underlying regulation of acid–base balance is not well understood. In fact, because digestion is associated with large

metabolic increments it is possible that the rise in $P_{a\mathrm{CO_2}}$ merely reflects an ineffective ventilatory compensation to the increased metabolic rate that fortuitously acts to regulate pHa. As an alternative, it has been suggested that increased $P_{a\mathrm{CO_2}}$ during digestion in humans is caused by the induction of a more relaxed state with low responsiveness to ventilatory stimuli (e.g. Higgins, 1914), as has been observed during sleep.

To study whether pHa or $P_{\mathrm{CO_2}}$ constitute the regulated variable during digestion, we used pharmacological inhibition of gastric acid secretion. We studied the snake *Boa constrictor* because it is able to ingest large meals and exhibits large postprandial ncreases in metabolism (Secor and Diamond, 2000; Toledo et al., 2003). Gastric acid secretion was inhibited by oral administration of the specific proton-pump inhibitor omeprazole. Omeprazole is a weak base with a pKa of about 4 that concentrates in acidic compartments, such as the secretory canaliculus of the parietal cells, where it undergoes an acid-catalysed transformation to a sulphonamide (Fellenius et al., 1981; Sachs et al., 1995; Huang and Hunt, 2001). The converted sulphonamide reacts with cysteine groups of the H^+,K^+-ATPase and leads to specific inhibition of gastric acid secretion (Fellenius et al., 1981; Sachs et al., 1995; Huang and Hunt, 2001). Hence, administration of omeprazole should greatly diminish the postprandial rise in plasma HCO_3^-. If inhibition of the alkaline tide also abolishes the postprandial rise in $P_{a\mathrm{CO_2}}$, in spite of increased metabolism, it would appear that the relative hypoventilation normally observed during digestion represents regulation of pHa. If, however, $P_{a\mathrm{CO_2}}$ increases in the absence of an alkaline tide, it would seem that the postprandial period is associated with a state-dependent increase in the $P_{a\mathrm{CO_2}}$-set-point for ventilatory regulation.

Materials and methods

Animals

Experiments were performed on 22 specimens of *Boa constrictor* L. that had been bred and reared in captivity for approximately 2 years at the Jacarezario at UNESP, Rio Claro (SP, Brazil). During this period, they were fed a mixed diet of rodents and chickens, and experienced temperatures of 22–32°C under a natural light cycle. All animals appeared healthy and had been fasted for 2–3 weeks before the experiments were conducted. The study consisted of two series of experiments performed on separate groups of snakes. For the first experiment (conducted in October, 2001), we measured arterial blood composition prior to and during digestion of six untreated snakes and six snakes treated with omeprazole (1.62±0.21 and 1.86±0.46 kg, respectively). For the second experiment (performed in August 2002), we determined the rate of oxygen uptake prior to and during digestion of five untreated snakes and five snakes treated with omeprazole (0.17±0.02 and 0.56±0.10 kg, respectively).

Administration of omeprazole

Eleven snakes were treated with omeprazole to inhibit gastric acid secretion. Omeprazole was dissolved in methylcellulose (1.5%) and administrated orally through a soft rubber tube inserted into the stomach through the mouth. We applied a dose of 60 μmol kg^{-1} (22 mg kg^{-1}, given as 2 ml kg^{-1} snake) every 48 h for 8 days (i.e. four administrations). A final dose was administered a few hours before feeding.

Measurements of the rate of oxygen uptake during digestion

Rates of O_2 uptake ($\dot{V}_{\mathrm{O_2}}$) were measured during fasting and after ingestion in a group of untreated animals and a group of snakes treated with omeprazole. Both groups ingested rodent meals of 30±3% of their body mass. Having determined the mass of the fasting snakes, they were placed in hermetically closed respirometers with a volume of 1–1.5 l maintained within a climatic chamber (Fanem, SP, Brazil) kept at 30°C throughout the experiment. $\dot{V}_{\mathrm{O_2}}$ of individual snakes was measured continuously for no less than 24 h prior to feeding. This period provided stable and repeatable values for $\dot{V}_{\mathrm{O_2}}$ that were averaged to obtain resting metabolic rate (RMR). Occasional high values for $\dot{V}_{\mathrm{O_2}}$ that reflected spontaneous activity were eliminated. Following respirometry, the chambers were opened and the snakes were offered live rats that they readily killed by constriction. Following ingestion, the metabolic measurements were continued until $\dot{V}_{\mathrm{O_2}}$ had returned to RMR levels.

$\dot{V}_{\mathrm{O_2}}$ was measured by an automised, intermittently closed, respirometry system (Sable System, TR-RM8; Salt Lake City, UT, USA). Briefly, the system was programmed to ventilate each respirometer with fresh air (open phase) for 70 min, while measuring the rate of oxygen depletion during a 10 min closed phase while dry air (water vapour had been removed with drierite) was re-circulated through an oxygen analyser (PA-1, Sable System). The output from the gas analyser was collected on data acquisition system (Sable System, DATACAN V) and $\dot{V}_{\mathrm{O_2}}$ was calculated from the rate at which the oxygen concentration decreased during the closed phase. The rate of decay was linear, with r^2 >0.9.

During digestion, body mass increases as food is assimilated. To calculate mass-specific $\dot{V}_{\mathrm{O_2}}$ rates, we assumed that assimilation amounted to 50% of the ingested meal and that the snake's body mass increased linearly over the initial 10 days (for a discussion of these assumptions, see Overgaard et al., 2002).

Arterial cannulation

Six untreated and six omeprazole-treated snakes were surgically catheterised for determination of arterial blood gases. The surgery was performed under CO_2 anaesthesia (see Wang et al., 1993). When the animals no longer responded to pinching of the skin, the vertebral artery or the caudal portion of the dorsal aorta was accessed through a 5 cm ventrolateral incision. The vessels were cannulated occlusively with PE90 containing heparinised saline and catheters were excised through the back and secured to the skin with sutures. This procedure took 20–30 min and all animals appeared to regain normal activity levels within an hour after surgery. Each snake was given an intraperitonial injection of antibiotic enrofloxacin

(Baytril®; 2–3 mg kg^{-1}) to prevent infection and was allowed to recover for a minimum of 18 h at 30°C before blood samples were taken.

Experimental protocol for blood gas determinations during digestion

Snakes were maintained individually within plastic boxes (60 cm×30 cm×15 cm) at 30±1°C (the preferred body temperature of *Boa constrictor*; McGinnis and Moore, 1969) within a temperature-controlled chamber. To minimise disturbance of the snakes, the catheters were passed through an opening in the top of the box and out of the climatic chamber at least 60 min prior to blood sampling. When blood samples had been collected from fasting snakes, each snake was fed a meal of freshly killed rats, which they struck and constricted before swallowing. The snakes normally ate two rats, and the meals constituted 28±7% (range 18–45%) of body mass. Some of the omeprazole-treated snakes did not eat voluntarily and had to be force-fed.

Measurements of arterial acid–base parameters, P_{O_2} and haematocrit

All blood samples (0.8–1.0 ml) were sampled anaerobically and analysed within 2 min after being collected. Blood pH was measured with a capillary pH electrode connected to a PHM 73 (Radiometer, Copenhagen, Denmark) maintained at 30°C in a BMS Mk 3 electrode unit (Radiometer). The pH electrode was calibrated several times a day with Radiometer precision buffers (S1500 and S1510). Total CO_2 content of freshly separated plasma ($ct[CO_2]_{pl}$) was measured according to Cameron (1971). Arterial P_{CO_2} (Pa_{CO_2}) was calculated using the rearranged Henderson–Hasselbalch equation:

$$Pa_{CO_2} = ct[CO_2]_{pl} / [\alpha_{CO_2} \times (1+10^{(pH-pK')})] , \quad (1)$$

using a CO_2 solubility in the plasma (α_{CO_2}) of 0.0366 mmol l^{-1} mmHg^{-1} (Heisler, 1986) and the apparent pK′ determined for *Python* plasma at 30°C (pK′= 0.0763×pH+6.7283; Overgaard and Wang, 2002). Plasma bicarbonate concentration ($[HCO_3^-]$) was then calculated as:

$$[HCO_3^-] = ct[CO_2]_{pl} - (Pa_{CO_2} \times \alpha_{CO_2}) . \quad (2)$$

Pa_{CO_2} was measured at 30°C with a Radiometer E5046-0 O_2 electrode maintained and calibrated at 30°C in the BMS Mk3 electrode assembly. The zero reading of the P_{O_2} electrode was verified daily by flushing the chamber with pure nitrogen and it was calibrated using humidified room air before each measurement. Haematocrit was determined following 3 min centrifugation at 12 000 revs min^{-1} in capillary tubes.

Data analysis and statistics

Effects of digestion on blood gas composition and oxygen consumption, within each set of experimental treatments, were analysed with a one-way analysis of variance (ANOVA) for repeated measures, followed by a *post hoc* Student–Newman–Keuls test to identify means that were significantly different. Differences in fasting values for untreated control snakes and snakes treated with omeprazole were compared with a Student's *t*-test. A Student's *t*-test was also used when comparing maximal metabolic changes during digestion in untreated and omeprazole-treated snakes. Differences were considered to be statistically significant when $P<0.05$ and all results are presented as means ± 1 S.E.M.

Results

The metabolic response to digestion for untreated and omeprazole-treated *Boa* is shown in Fig. 1. RMR of untreated animals was 1.63±0.32 ml O_2 kg^{-1} min^{-1}, which was significantly higher than RMR of omeprazole-treated snakes (0.81±0.14 ml O_2 kg^{-1} min^{-1}). In both groups of snakes, digestion was associated with a three- to fourfold increase in metabolic rate compared to fasting levels. Peak metabolic rate occurred about 20 h later in the omeprazole-treated animals.

Plasma HCO_3^- concentration of untreated control animals increased from a fasting level of 13.9±1.0 mmol l^{-1} to 25.9±0.9 mmol l^{-1} within 12 h after ingestion and remained elevated for the remainder of the experiment (Fig. 2, open symbols). Arterial pH of fasting untreated control animals was 7.519±0.016, and increased significantly to a maximal value of 7.641±0.014 at 24 h after ingestion. Digestion was also associated with a significant increase in Pa_{CO_2} from a fasting level of 16.3±0.9 to 26.4±1.1 mmHg at 12 h post feeding. Using a Davenport diagram (Fig. 3), we estimate that pHa would have increased to approximately 7.75 if Pa_{CO_2} had remained at the fasting level during digestion (see red line in Fig. 3). Conversely, to maintain pHa of the fasting level, Pa_{CO_2} would have had to increase to 34 mmHg (see blue line in Fig. 3).

Fig. 2 also includes the arterial acid–base parameters of the omeprazole-treated animals. The fasting acid–base parameters

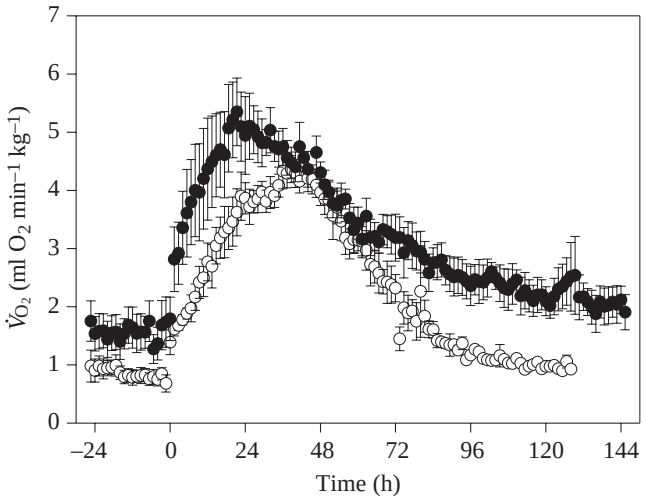

Fig. 1. Temporal changes rate of in oxygen uptake ($\dot{V}_{O_2}$) in *Boa constrictor* before and after ingestion of a meal in untreated control animals (solid circles) and snakes treated with omeprazole to inhibit gastric acid secretion (open circles). The prey was ingested at time 0 h. Values are means ± 1 S.E.M. (N=5 in each group).

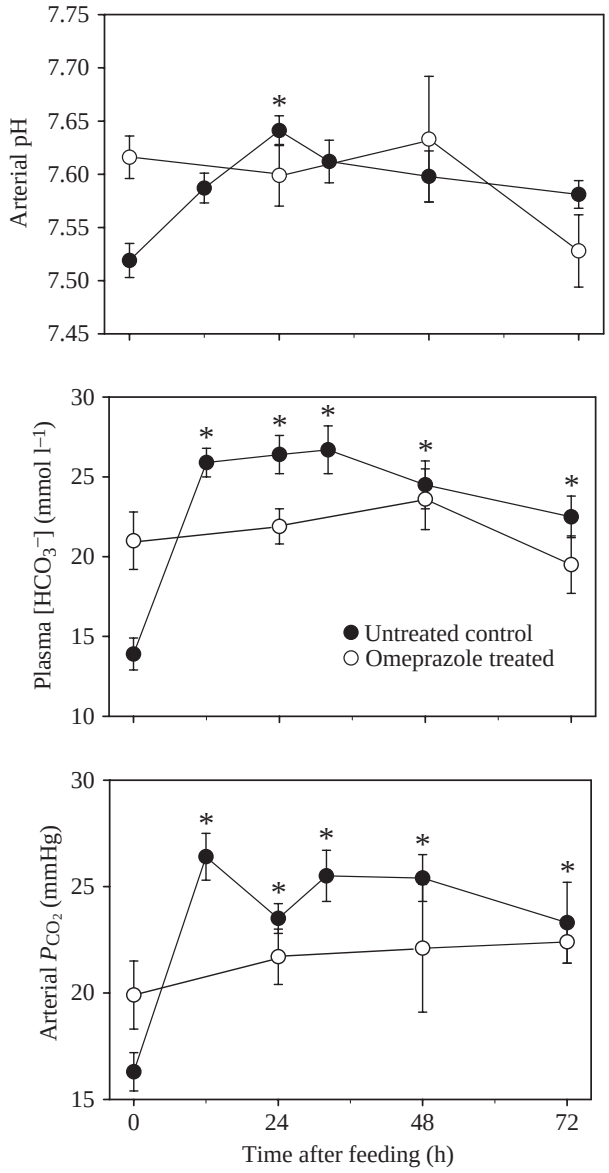

Fig. 2. Acid–base parameters of arterial blood before and following feeding in *Boa constrictor* after ingestion of a meal in untreated control animals (solid circles) and snakes treated with omeprazole to inhibit gastric acid secretion (open circles). (A) pHa, arterial pH; (B) $[HCO_3^-]_{pl}$, plasma $[HCO_3^-]$; (C) and Pa_{CO_2}, arterial P_{CO_2}. The values obtained from fasting animals are presented at 0 h. Values are means ± 1 S.E.M. (N=5–7), and mean values that are significantly different (P<0.05) from the fasting value are marked with an asterisk. 1 mmHg=0.133 kPa.

of this group of snakes differed somewhat from the control group. Thus, the omeprazole-treated animals had a significantly higher pHa (7.616±0.020) as well as significantly higher Pa_{CO_2} and plasma $[HCO_3^-]$ (19.9±1.6 mmHg and 21.0±1.8 mmol l^{-1}, respectively) compared with untreated snakes. Following ingestion, there were no significant changes in pHa, and there only very small, and not statistically significant, increases in Pa_{CO_2} and plasma $[HCO_3^-]$ (Fig. 2).

There were no changes in arterial P_{O_2} or haematocrit during digestion in any of the two experimental groups (Table 1), but haematocrit values of the untreated control snakes were significantly higher than those of the omeprazole-treated snakes.

Table 1. *Arterial* P_{O_2} *and haematocrit of the snake* Boa constrictor *before and after ingestion of a meal in untreated snakes and snakes treated with omeprazole to inhibit gastric acid secretion*

	Untreated snakes		Omeprazole-treated snakes	
	Pa_{O_2} (mmHg)	Haematocrit	Pa_{O_2} (mmHg)	Haematocrit
Fasting	61.1±2.7	26.0±1.5	60.9±2.0	19.2±0.9
Postprandial (h)				
12	63.5±3.1	23.1±1.8		
24	56.1±2.6	22.5±2.1	70.4±3.9	19.7±0.7
32	59.7±2.6	21.9±2.3		
48	58.9±5.1	25.0±1.5	63.6±4.9	20.1±1.1
72	54.9±5.8	25.0±2.0	60.9±2.0	19.2±0.9

Pa_{O_2}, arterial P_{O_2}.
Values are means ± 1 S.E.M. (N=5–7 in each group).
1 mmHg=0.133 kPa.

Discussion

Our aim was to investigate whether the increased Pa_{CO_2}, normally associated with digestion, represents a compensatory response to increased plasma HCO_3^- concentration (i.e. the alkaline tide). Gastric acid secretion, and hence the alkaline tide, was inhibited with omeprazole, a well-known specific inhibitor of the H^+,K^+-ATPase in mammals (e.g. Sachs et al., 1995). While omeprazole does inhibit gastric acid secretion in amphibians (Starlinger et al., 1986; see also Andersen et al., 2003), it is unknown whether it has an equally potent role in reptiles. Nevertheless, the complete ablation of the alkaline tide demonstrates that acid secretion was reduced to an extent where strong ion difference of the blood was unaffected by digestion. However, because we did not measure pH in the gastric lumen, we cannot ascertain that gastric acid secretion was fully blocked. Although omeprazole exerts an almost irreversible inhibition of the proton pumps, it only binds to actively secreting pumps that are inserted in the membrane (e.g. Sachs, 1997; Huang and Hunt, 2001). Gastric acid secretion of *Boa* in the present study may, therefore, have been restored by insertion of new proton pumps later in the digestive period.

The metabolic response to digestion

Boa exhibited the well-established rise in oxygen uptake after feeding (e.g. Benedict, 1932; Secor and Diamond, 1995, 2000; Andrade et al., 1997). Oxygen uptake of untreated snakes increased three-to fourfold and reached maximal levels of 4–6 ml O_2 kg^{-1} min^{-1}. The factorial increase and the peak rates are somewhat lower than most values reported for *Boa constrictor* and *Python molurus* following similar meal sizes

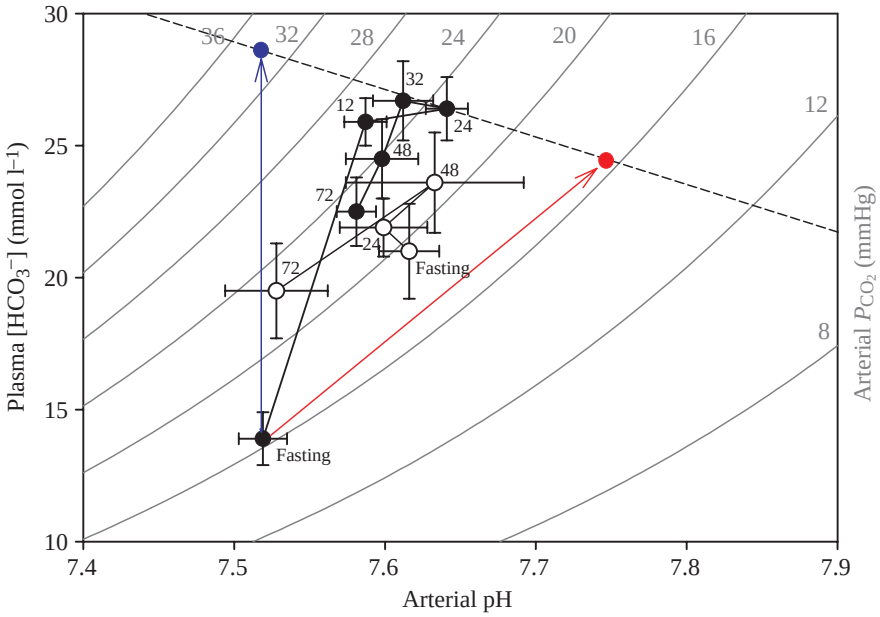

Fig. 3. Davenport diagram with calculated P_{CO_2} isoclines showing changes in extracellular acid–base status of *Boa constricta* when fasting and during digestion. Numbers indicate time (h) after digestion. Untreated control snakes, solid circles; omeprazole-treated snakes, open circles. For comparison, acid–base values predicted in the case of no ventilatory compensation (i.e. maintained Pa_{CO_2}) are shown in red, while the predicted acid–base status in case of a maintained pHa is shown in blue. The dotted line represents the non-bicarbonate buffer line obtained on *Python molurus* (Overgaard and Wang, 2002).

at 30°C (Secor and Diamond, 1995; Overgaard et al., 1999, 2002; Secor et al., 2000; Toledo et al., 2003). The lower factorial scope is, at least partially, due to the relatively high RMR in our study compared to previous measurements on *Boa* (Chappell and Ellis, 1987; Secor and Diamond, 2000; cf. Toledo et al., 2003), but maximal $\dot{V}_{O_2}$ during digestion was lower than reported by Secor and Diamond (2000) (see also Toledo et al., 2003).

RMR was lower in omeprazole-treated snakes, but because the untreated snakes had a lower mass than the omeprazole-treated snakes, it is unlikely that the difference in RMR is due a direct effect of omeprazole. Omeprazole-treated animals were able to digest the ingested prey and the factorial increase in metabolism was similar to that of untreated animals. However, maximal $\dot{V}_{O_2}$ occurred somewhat later in omeprazole-treated snakes, which may reflect a lower rate of food degradation within the stomach in the absence of acid secretion. In mammals, the rate and efficiency of digestion is not markedly affected by omeprazole (e.g. Evenopoel, 2001), and it has been suggested that gastric acid secretion is more important for reducing infections transmitted over the gut than for digestion (e.g. Sanford, 1992). However, in snakes and other animals that ingest large and intact prey, it seems likely that gastric acid secretion serves an important role in digestion and by initiating the breakdown of the large meals within the stomach.

Secor (2003) recently estimated that gastric production and secretion of HCl and enzymes account for more than half of the energetic costs of digestion in *Python*. In this case, one would expect that inhibition of gastric acid secretion should significantly reduce SDA of omeprazole-treated snakes. However, since it is possible that gastric acid secretion was restored later into the digestive period, our study may not be able to reveal anything about the costs of gastric function during digestion.

Effects of digestion on arterial acid–base parameters and oxygen levels

The changes in arterial acid–base balance during the postprandial period are consistent with previous studies on snakes and other ectothermic air-breathing vertebrates (Wang et al., 1995, 2001; Overgaard et al., 1999; Busk et al., 2000a,b; Overgaard and Wang, 2002; Andersen and Wang, 2003). Plasma HCO_3^- concentration of untreated snakes increased by approximately 13 mmol l^{-1} (Fig. 2). This is larger than the 6 mmol l^{-1} increase that has been observed previously in similarly-sized *Python* (Overgaard and Wang, 2002; see also Overgaard et al., 1999), but similar to that observed in *Alligator*, *Rana* and *Bufo* (Busk et al., 2000a,b; Andersen and Wang, 2003). The alkaline tide of *Boa* lasted considerably longer than in *Python*, where most of the acid–base changes occur within the first 48 h after ingestion (Overgaard et al., 1999). The magnitude of the alkaline tide represents the temporal and quantitative difference in gastric acid secretion and the subsequent base output by the pancreas and the intestine when food is passed from the stomach to the intestine. It is possible that *Boa* and *Python* differ in the speed at which these processes proceed. Indeed, it seems that *Python* does pass a larger portion of meal to the intestine within the initial 24 h of digestion compared to *Boa* (Secor and Diamond, 2000).

In spite of the increased plasma HCO_3^- concentration, pHa only increased by 0.12 pH units because the elevated Pa_{CO_2} countered the metabolic alkalosis. A similar pattern has been observed in all studies on amphibians and reptiles where blood samples were obtained through chronic cannulation on minimally disturbed animals (Wang et al., 1995, 2001; Overgaard et al., 1999; Busk et al., 2000a,b; Overgaard and Wang, 2002). A smaller, but qualitatively similar respiratory compensation, has also been observed in cats (Ou and Tenney, 1974) and humans (e.g. Higgins, 1914; Erdt, 1915; Van Slyke et al., 1917). The increased Pa_{CO_2} seems to be caused by a

relative hypoventilation, where lung ventilation does not increase proportionally to CO_2 production (Glass et al., 1979; Wang et al., 1995; Hicks et al., 2000; Secor et al., 2000). We have previously speculated that the relative hypoventilation implies that amphibians and reptiles control pHa and not $P_{a_{CO_2}}$ during the postprandial period (e.g. Wang et al., 2001).

The relatively low $P_{a_{O_2}}$ of *Boa* is common for reptiles and can be explained by admixture of systemic venous blood to the arterial blood within the undivided ventricle (Right-to-Left (R–L) cardiac shunt; e.g. Wang and Hicks, 1996). The sizable R–L cardiac shunt of reptiles means that $P_{a_{CO_2}}$ and $P_{a_{O_2}}$ are determined by different parameters, so that $P_{a_{CO_2}}$ can increase without concomitant decreases of $P_{a_{O_2}}$. Thus, because the capacitance of CO_2 in blood is much higher than that of oxygen, $P_{a_{CO_2}}$ is primarily determined by lung P_{CO_2}, whereas $P_{a_{O_2}}$ is primarily determined by the degree of admixture and venous oxygen levels (reviewed by Wang and Hicks, 1996; Wang et al., 2001).

Effects of inhibiting gastric acid secretion on arterial acid–base status during fast and digestion

Fasting omeprazole-treated animals had higher pH, $P_{a_{CO_2}}$ and plasma HCO_3^- concentration than untreated control snakes. While this may be a direct effect of omeprazole on acid–base balance of fasting animals, it may also be caused by seasonal changes since the two sets of experiments were conducted at different times of the year. In rats, omeprazole treatment over several months does not affect arterial acid–base status (T. Wang, P. Norlen and R. Haakanson, personal observation). Irrespective of the differences in acid–base status of fasting snakes, omeprazole greatly reduced the changes in arterial acid–base parameters seen during digestion. The marked reduction of the alkaline tide is consistent with omeprazole being effective in blocking gastric acid secretion. If gastric acid secretion was completely blocked by omeprazole, it may have been expected that the snakes would display a postprandial decrease in plasma HCO_3^- concentration (i.e. decreased SID) as pancreatic base production is stimulated by the entrance of chyme to the intestine. Part of the increased pancreatic base output during digestion occurs in response to acidification of the small intestine, but in some mammals, the base output increases even when gastric acid secretion is inhibited (Vaziri et al., 1980). As discussed previously, we cannot ascertain whether gastric acid secretion was fully blocked and it is possible that the stable plasma HCO_3^- concentration throughout digestion reflect equimolar gastric acid output and pancreatic base secretion.

Inhibition of gastric acid secretion and the alkaline tide abolished the postprandial increase in $P_{a_{CO_2}}$ even though metabolic rate increased similarly to untreated control snakes (Fig. 1). Thus, the increased $P_{a_{CO_2}}$ during digestion is not caused by inefficient ventilatory response to elevated metabolism, or a more relaxed state during the postprandial period (Higgins, 1914). Instead, our data strongly suggest that the ventilatory compensation of the alkaline tide represents a regulated response that serves to maintain pHa and not $P_{a_{CO_2}}$.

The ventilatory responses to acid–base disturbances in reptiles are complex and involve different receptors (e.g. Milsom, 1995), and all of these may be involved in the respiratory compensation during digestion. It is not well known whether reptiles regulate pH or P_{CO_2}, but immediately after an acutely imposed acidosis by exercise or infusion of lactic acid in resting lizards, it seems that ventilation is geared towards regulation of $P_{a_{CO_2}}$ (Mitchell and Gleeson, 1985). However, with chronic alkalosis by systemic infusion of bicabonate, pHa seems to be regulated (Jackson, 1969). Central chemoreceptors exert an important contribution to ventilatory responses to acid–base disturbances in reptiles (Hitzig and Jackson, 1978; Branco and Wood, 1993). In mammals, the central chemoreceptor is not as sensitive to metabolic acid–base disturbances of arterial blood as they are to respiratory disturbances, because the blood–brain barrier, separating blood from the cerebrospinal fluid (CSF), is rather impermeable to ions, but permeable to CO_2 (e.g. Fencl, 1986). It is likely that a similar mechanism operates in reptiles, but the slow time course of the alkaline tide may allow for the metabolic alkalosis to be transmitted from the blood to the CSF. Alternatively, it is possible that pH-sensitive peripheral chemoreceptors contribute to the ventilation compensation. Finally, elevated lung and end-tidal P_{CO_2} during digestion may stimulate lung and upper airway receptors that may regulate ventilation whenever metabolic rate is increased (e.g. Furilla, 1991; Furilla et al., 1991). Clearly the role of the different receptors needs to be further understood to provide a mechanistic explanation of the regulation of arterial pH during digestion in snakes.

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