The Journal of Experimental Biology 208, 3047-3053
Published by The Company of Biologists 2005
doi:10.1242/jeb.01746

Structure and function of the esophagus of the American alligator (*Alligator mississippiensis*)

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Accepted 13 June 2005

Summary

Esophageal structure and function were studied in juvenile American alligators (*Alligator mississippiensis*). The anatomy of alligators differs from humans in several important aspects: the crocodilian esophagus is more muscular and is composed entirely of smooth muscle. Functionally, the crocodilian esophagus is similar to that of mammals, but alligators have peak esophageal peristaltic pressures that are 2–3-fold greater than pressures in the human esophagus. As is found in humans, the incidence of esophageal reflux increased in postprandial animals compared with the fasting state. We observed a large increase in pressure in the lower esophageal sphincter (LES) during ventilation that ranged from 200% to 3000% of the pressures measured during apnea. These pressure changes appear to be intrinsic to the LES. Alligators lack a mammalian-type diaphragm; thus, there is no crural diaphragmatic contribution to LES pressure. These features recommend the alligator as a useful model for the study of regulation of the LES.

Key words: lower esophageal sphincter, peristalsis, animal model, alligator, esophagus.

Introduction

Reptiles have been suggested to be useful models for the study of regulation of the gastrointestinal system for several reasons (Secor and Diamond, 1998). First, their regulatory responses are easier to examine experimentally than those of the typical mammalian models because they have extreme responses to feeding. Many reptiles consume huge meals (up to 160% of their own body mass) at infrequent intervals (sometimes fasting for 18 months). By contrast, most mammalian model species (i.e. rats, mice, rabbits, pigs, etc.) eat small meals very frequently. Hence, reptiles that consume infrequent meals have correspondingly larger regulatory responses to feeding than do mammals. Second, studying the digestive responses of reptiles improves our understanding of the evolution of the regulatory mechanisms of the gastrointestinal tract. Although previous research on the digestive responses of reptiles has examined regulatory phenomena such as hormone release, the growth and atrophy of organs, and acid–base homeostasis (Andrade et al., 2004; Busk et al., 2000; Pennisi, 2003; Secor and Diamond, 1995, 1998; Secor et al., 2001; Starck, 1999; Starck and Beese, 2001, 2002; Starck et al., 2004), less attention has been directed at using reptilian models to advance our understanding of regulation of the esophagus and stomach (Secor, 2003).

The aim of our study was to examine the structure and function of the esophagus of juvenile American alligators (*Alligator mississippiensis*) and to compare this anatomy and physiology with that of typical mammalian models. We found that the underlying function and control of the esophagus is similar in alligators and mammals (including humans) but that the esophageal musculature is thicker and the strength of esophageal peristaltic waves considerably stronger in the alligator when compared with the human. Furthermore, regulatory responses of the lower esophageal sphincter (LES) were larger by several orders of magnitude in alligators than in mammals. These large responses and anatomical differences (e.g. the lack of a mammalian-type diaphragm) may render the alligator a useful model species to study the regulation of esophageal performance, particularly the LES. Understanding the mechanisms required to coordinate esophageal function with other organ systems is of clinical importance because of the high incidence of the co-existence of gastroesophageal reflux disease (GERD) and respiratory diseases (e.g. asthma, emphysema) (Harding, 1999; Theodoropoulos and Ledford, 2000).

Materials and methods

Animals

Five juvenile American alligators (*Alligator mississippiensis* L.) ranging in body mass from 0.5 to 2.0 kg were held in aquaria (200–3600 liters) at 30±1°C with a 12 h:12 h L:D photoperiod. Animals were fed *ad libitum* weekly on a mixed diet of mice, smelts and crickets. Before each experiment (with

the exception of the reflux study), the animals were fasted for 14 days. All experiments were conducted on unanesthetized animals resting in the prone position at room temperature (20–22°C). An additional animal was used to study the histology of the esophagus.

Histology

One alligator (2.5 kg) was euthanized and immediately exsanguinated and embalmed with 10% neutral-buffered formalin. Tissues were sampled from the proximal (pharyngeal or cranial), middle and distal (gastric or caudal) esophagus. Samples were embedded in paraffin and cut in longitudinal sections 4 μm thick. The sections were stained with hematoxylin and eosin. The distal sample included the lower esophageal sphincter (LES). Samples were analyzed using a light microscope. Photographs were taken with a digital camera.

Esophageal peristalsis

A Polygraph HR (Medtronics, Minneapolis, MN, USA) water perfusion system, inserted orally, with a four-port probe (each port 1 cm apart) was used to measure peristaltic waves in the esophagus. Water flowed from the ports at 1 ml s^{-1}. The speed of propagation of each peristaltic wave was determined as the time that the leading edge of each wave passed from the proximal (pharyngeal or cranial end) to distal (gastric or caudal end) port (4 cm). Data were recorded with a Polygram Windows software package (Medtronics).

Esophageal reflux

Two solid-state pH electrodes (Medtronics), inserted orally, were used to measure the pH of the esophagus 3 cm proximal (craniad) to the LES and of the stomach 3 cm distal (caudad) to the LES. Each probe was calibrated with pH 4 and 7 buffers prior to insertion into the animals. At the end of the experiment, the probe was removed and the calibration checked using pH 4 and 7 buffers. After fasting for one week, the pH was monitored for a period of 24 h. The sensors were then removed for approximately 10 min while each of the animals consumed a meal of mice weighing 3% of the alligator's mass. The probes were reinserted and esophageal and gastric pH were monitored for 48 h postprandially. A bout of reflux was defined as a drop in esophageal pH below 4.

Ventilation

Ventilation through a mask placed over the nares was measured with a pneumotach (model 8311; Hans Rudolph, Inc., Kansas City, MO, USA). The mouth was sealed except for a small port through which the pH electrodes and pressure transducers were passed.

LES manometric technique

Two pressure transducers (model SPR-524; Millar MikroTip, Houston, TX, USA) 1 cm apart were attached to a pH electrode (Medtronics). The caudad pressure transducer was adjacent to the pH sensor. PE 90 tubing was also attached 4 cm craniad to the pH sensor in order to administer a bolus of water into the esophagus. The sensors were slipped through the mouth and past the velum palatinum, a transverse fold descending from the palate that completely shuts off the oral cavity from the esophagus (Reese, 1915), and into the stomach. Pressure and pH measurements were made at 1-cm intervals while the transducer was pulled cephalad until reaching the LES, at which time pressure and pH measurements were made at 0.5-cm intervals. After passing through the LES, measurements at 1-cm intervals were resumed. Once the position of the LES was determined from the pressure profile, the transducers were returned to the following four positions to collect data during both apneic and ventilatory periods: (1) the distal pressure transducer was located in the stomach while the proximal transducer was located in the LES, (2) both transducers were positioned within the LES, (3) the distal transducer was positioned within the LES whereas the proximal transducer was positioned in the esophagus and (4) both transducers were positioned within the esophagus. A 2 ml intraesophageal bolus of water was used to stimulate deglutition and relaxation of the LES.

Data acquisition

For all experiments except the studies of peristalsis, analog signals were converted to digital using a BioPac System (Goleta, CA, USA) and analyzed with AcqKnowledge software (BioPac). Data were collected at 50 Hz.

Results

Histology

Our histological examination of the alligator esophagus is in good agreement with the anatomical description of Reese (1915). We found the alligator esophagus to contain a mucosa, a muscularis mucosa that runs longitudinally, a middle circular muscle layer and an outer longitudinal muscle layer. Myenteric plexi are present between the muscle layers. We found no striated muscle in the esophagus. These features are shown in longitudinal section of the mid-esophagus in Fig. 1. A cross-section of the distal (caudad) esophagus, in the region of the high-pressure zone (LES), is shown in Fig. 2. The zone is characterized by increased muscle thickness of all layers in the region. The mucosal lining of the esophagus is composed of ciliated columnar cells in the proximal (craniad) and mid portions of the esophagus, although cilia were sparse to absent in the distal esophagus. Mucous secreting cells were also observed, as shown in Fig. 3.

Esophageal peristalsis

All animals exhibited characteristic peristaltic waves while swallowing. The speed of wave propagation was 0.56±0.43 cm s^{-1} (mean ± S.E.M., N=5). The peak pressure at each port for a peristaltic wave for one swallow per animal is reported in Table 1. Fig. 4 illustrates esophageal pressure measurements in an alligator during peristalsis.

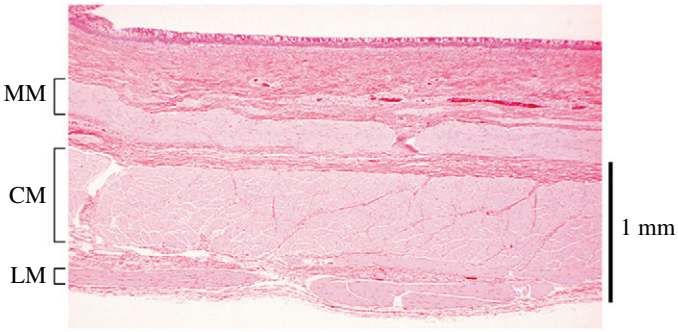

Fig. 1. Longitudinal-section at the mid-esophageal level. The crocodilian esophagus exhibits three muscle layers: muscularis mucosa (MM), circular muscle (CM) and outer longitudinal muscle (LM) layer of the muscularis propia.

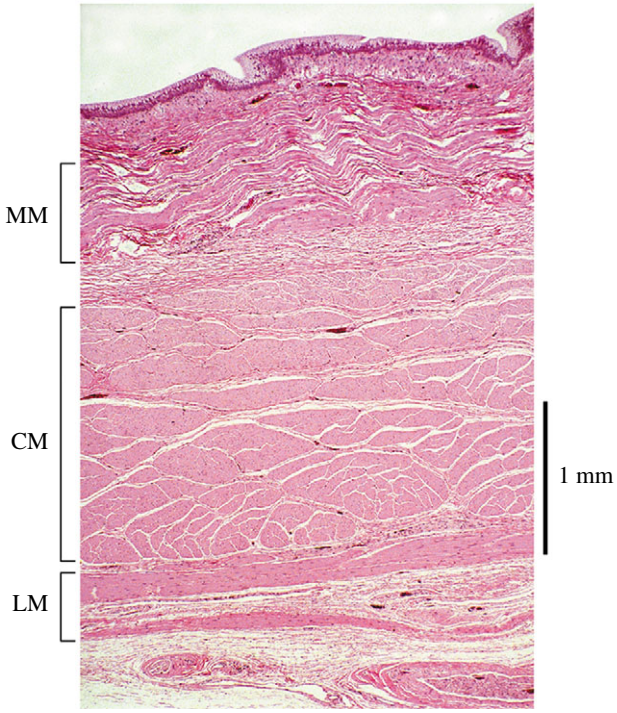

Fig. 2. Longitudinal-section at the distal esophageal level in the region of the high-pressure zone. Note the increased muscle thickness in all layers when compared with the mid-esophagus (Fig. 1).

Esophageal and gastric pH of fasting alligators

pH of the esophagus and stomach of fasting alligators (N=5) was 6.33±0.06 and 3.31±0.23, respectively.

Esophageal reflux

The percentage of time that esophageal pH was less than or equal to 5.5, 5.0, 4.5 and 4.0 is reported in Table 2 for both the 24 h preprandial period and the 48 h postprandial period. One of five animals showed esophageal reflux where the pH dropped to 4.0 or less, which occurred for 11.3% of the postprandial period.

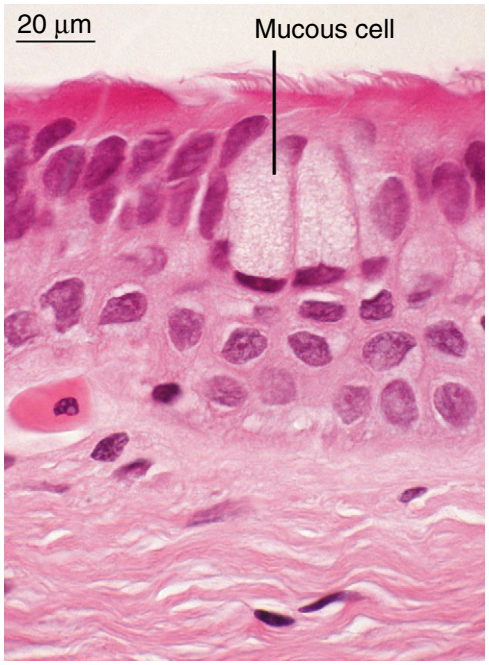

Fig. 3. Section of the inner mucosa at the mid-esophagus level. Note the ciliated columnar epithelium at the surface as well as two large mucous cells. In addition, a nucleated red blood cell can be seen on the left margin, mid-section.

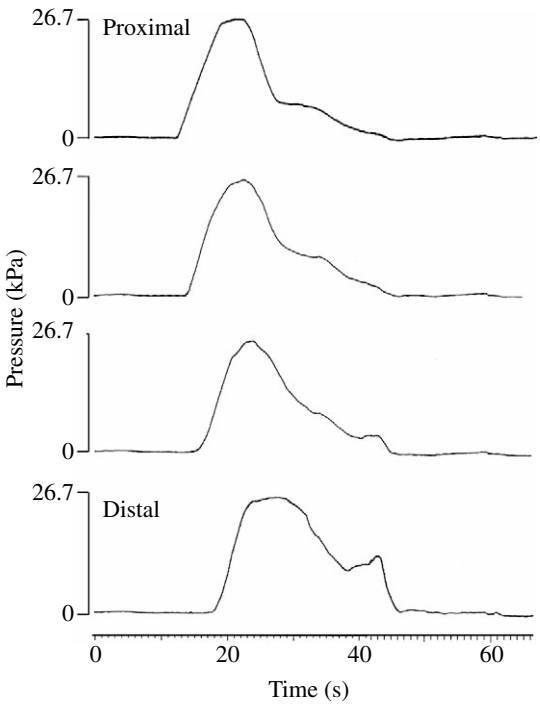

Fig. 4. A sample of data from one animal. The esophageal peristaltic wave was stimulated with a bolus of water.

LES, gastric and esophageal pressures, and ventilation

Nonventilatory, resting pressures of the LES were measured to be either lower or within the range of normal human LES

Table 1. *Resting intraesophageal and peak peristaltic wave pressures*

	Port 1 (proximal)		Port 2		Port 3		Port 4 (distal)	
Alligator	Peak	Resting	Peak	Resting	Peak	Resting	Peak	Resting
1	46.0	1.6	41.3	1.5	32.0	2.0	12.7	1.3
2	29.3	1.3	30.7	1.3	40.0	1.3	32.7	1.3
3	26.7	1.3	25.3	0.3	25.3	1.3	25.3	1.3
4	12.0	2.7	12.7	2.2	15.3	2.7	10.7	2.7
5	12.7	2.0	12.0	1.1	11.3	2.0	15.3	2.0
Means ± S.E.M.	25.3±6.3	1.8±0.3	24.4±5.6	1.3±0.3	24.8±5.3	1.9±0.2	19.3±4.2	1.7±0.3

Pressures (kPa) were recorded with a water perfusion system. The probe was placed in the esophagus. It contained four ports spaced at 4 cm intervals along the length of the probe.

Table 2. *Fasting and postprandial esophageal reflux data*

	Alligator 1		Alligator 2		Alligator 3		Alligator 4		Alligator 5	
Esophageal pH	Fasting	Fed	Fasting	Fed	Fasting	Fed	Fasting	Fed	Fasting	Fed
⩽5.5	6.5	61.1	0	0	19.4	3.4	1.7	14.8	2.3	0
⩽5.0	3.3	47.7	0	0	7.5	1.2	0	6.9	0	0
⩽4.5	0	24.6	0	0	1.3	0	0	3	0	0
⩽4.0	0	11.3	0	0	0	0	0	0	0	0

Values reported in the table are the percentage of time that esophageal pH was either equal to or less than the value of pH reported in the far left-hand column for a 24 h period of fasting and 48 h postprandial (fed) period.

pressures (1.3–4.7 kPa). During a period of ventilation, LES pressure increased significantly. A sample of the data collected when both the proximal and distal pressure sensors were within the LES is provided in Fig. 5, and these data illustrate the large increase in LES pressure seen during ventilation. Fig. 6 illustrates data collected when the distal pressure transducer was within the stomach and the proximal transducer was within the LES. In contrast to the increase in pressure seen within the LES during ventilation, gastric pressure declined during ventilation compared with apnea. Similarly, esophageal pressures decreased rather than increased during ventilation compared with apnea. Additionally, Fig. 6 illustrates that when a bolus of water was given during a ventilatory bout, the reflex to swallow and relax the LES predominated over a rise in LES pressure.

Although a large rise in LES pressure (ranging from 200% to 3000%) was nearly always seen during ventilation, we did on rare occasions observe a bout of ventilation that was not accompanied by any increase in LES pressure.

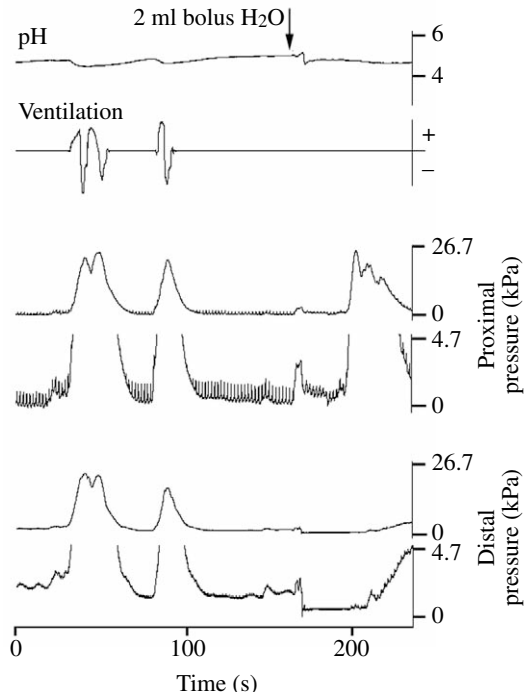

Fig. 5. Sample of data collected when both pressure probes were placed within the lower esophageal sphincter (LES). The top and second trace are recordings of the pH and ventilation, respectively. Ventilation begins with an exhalation (positive voltage) and ends with an inspiration. Thus, the apnea consists of a breath-hold. The third and fourth traces give the pressure from the most proximal (cranial) probe with a gross and fine pressure scale, respectively. Note that peak pressures during ventilation increased dramatically, in this case from a baseline of ~1.3 kPa to a peak of nearly 26.7 kPa. The small regular spikes in pressure seen in the fine scale are caused by the heartbeat. The fifth and sixth traces are the pressure recordings from the distal (caudal) probe with two pressure scales. The expanded pressure scale of the sixth trace shows most clearly the relaxation in pressure that occurred in the LES during a wet swallow (the arrow indicates the time a 2 ml bolus of water was given). This response to wet swallows was observed in all animals studied (*N*=5).

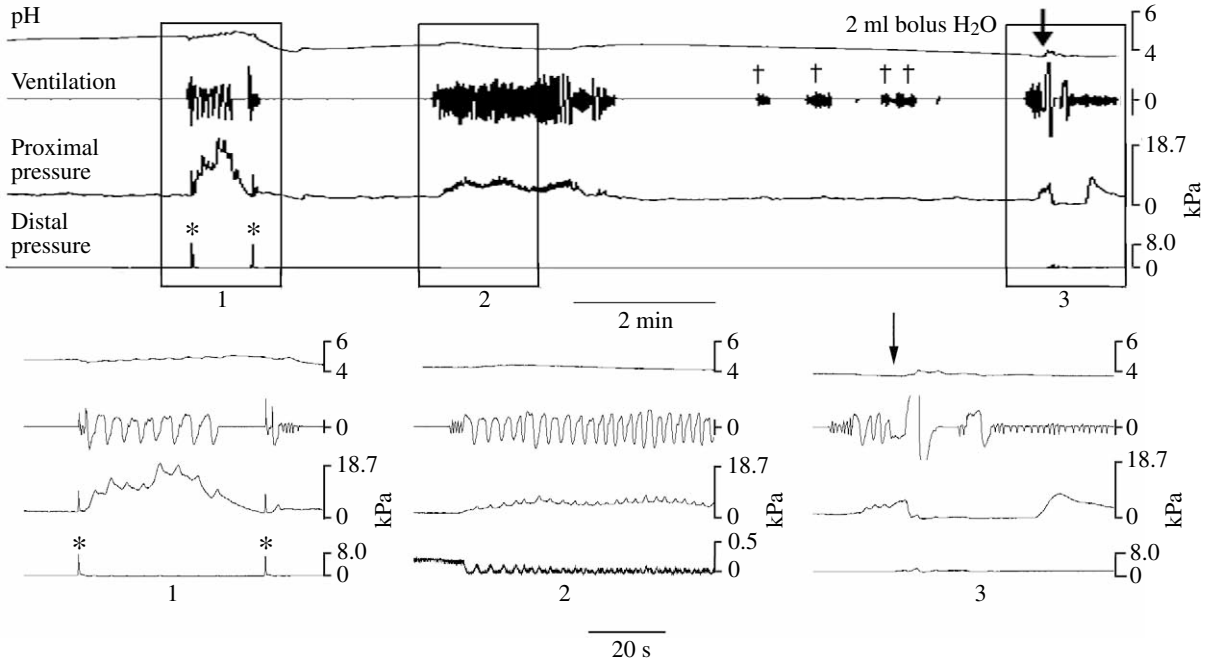

Fig. 6. Sample of data collected when the proximal (cranial) and distal (caudal) transducers were located within the lower esophageal sphincter (LES) and stomach, respectively. The top portion of the graph shows a time span of approximately 15 min and illustrates large rises in LES (proximal) pressure with ventilation. The two spikes in pressure marked with an asterisk were due to vocalization and a general elevation of pressure in the thoraco-abdominal cavity. These spikes demonstrate that the increase in LES pressure associated with ventilation is independent of any thoraco-abdominal pressure changes and is intrinsic to the LES. Fluctuations in the ventilatory trace that are marked with daggers are caused by gular flutter, where air is taken in and out of the gular cavity. This serves an olfactory but not a gas exchange function (Farmer and Carrier, 2000b). Note that there is no rise in LES pressure associated with the gular flutter. The bottom part of the figure shows panels 1, 2 and 3 in more detail. Note that the scale for the gastric pressure on panel 2 is also expanded. Although ventilation generally caused LES pressure to increase, it caused gastric pressures to decrease. This is because the glottis is closed during apnea and the respiratory muscles are relaxed, thus elevating thoraco-abdominal pressure (Farmer and Carrier, 2000a). Panel 3 shows a bout of ventilation that was interrupted by a 2 ml bolus of water (indicated by arrow). Note that the wet-swallow reflex predominated over the LES pressure increase.

Discussion

General features of the alligator esophagus

The mammalian esophagus differs from the crocodilian esophagus in the following features: (1) the mucosal lining of mammalian esophagus is composed entirely of squamous epithelia, as opposed to columnal epithelia, without cilia or mucous cells, although submucosal mucous glands are found in mammals; (2) the wall and muscle layers are thinner, with only two muscle layers represented (inner circular and outer longitudinal) and (3) the proximal one-third to one-half is formed of skeletal muscle, while the crocodilian esophagus is composed entirely of smooth muscle. An entirely smooth-muscled organ is reported to exist in the duck-billed platypus, amphibians, birds and other reptiles (Ingelfinger, 1958). However, more recent work has found striated muscle in the pharyngeal region of the esophagus in bullfrogs and African clawed frogs (Yoshida, 2001) and in the proximal esophagus of some birds (Geyikoglu et al., 2002).

The esophagus of alligators exhibited characteristic peristaltic waves, as found for humans. However, the mean velocity of esophageal peristalsis (0.56 cm s^{-1}) is considerably slower than that of humans (3–5 cm s^{-1}). Also, peak esophageal pressures were considerably higher in the alligator (mean of 19.3 kPa in the distal and 25.3 kPa in the proximal esophagus; Table 1) than in humans (typically 1.2–1.4 kPa in the distal esophagus and 0.9–1.1 kPa in the proximal esophagus).

The LES functions similarly in alligators and humans. For both, boli of water in the esophagus stimulate peristalsis and relaxation of the sphincter simultaneously. After a short period, the sphincter regains its tone, and pressure rises to levels equal to or greater than those observed before boli delivery and swallowing, as is observed with water boli in the human esophagus. We found episodes of reflux to be relatively rare in fasting alligators. As observed for mammals, the incidence of reflux increased in the postprandial period.

Coordination of respiration with LES function

Alligators experience large but variable increases in LES pressure during bouts of ventilation compared with apnea. The increase in pressure generally ranged from 200% to 3000%. However, on rare occasions, no pressure increase was seen coincident with ventilation. Fluctuations in LES pressure during apnea and ventilation have also been observed in anesthetized piglets (Kiatchoosakun et al., 2002). Kiatchoosakun et al. (2002) used hypoxia to stimulate

respiratory rate and found a peak increase in LES pressure of 49% (from a baseline of 0.65±0.09kPa to 1.0±0.12kPa). This increase in LES pressure was blocked by atropine, indicating cholinergic control of LES tone. A decline in LES pressure accompanied the development of apnea during a subsequent hyperoxic exposure. These authors suggest that a loss of respiratory neural output might contribute to the loss of LES tone. A cholinergic-dependent neuromuscular control of the LES is also observed in humans. Thus, the changes in pressure observed within the LES of the alligator may well be due to cholinergic-dependent neural control.

Although the patterns for neural control of ventilation and LES tone appear to be similar in mammals and alligators, alligators may have certain advantages as a model organism to study this phenomenon for the following reasons.

(1) Because alligators lack a crural diaphragm, it is unlikely that LES tone is greatly influenced by diaphragmatic contractions. The mammalian LES is closely associated with the crural part of the diaphragm, and diaphragmatic contraction exerts a sphincteric action on the LES (Mittal et al., 1988, 1990), although the diaphragmatic contribution to LES pressure has been controversial. Crocodilians have a muscle called the 'diaphragmaticus' but it is not homologous to the mammalian diaphragm. The crocodilian diaphragmaticus attaches the liver to the pelvic girdle and the posterior-most gastralia and facilitates inspiration; it does not insert on the esophagus (Gans and Clark, 1976; Reese, 1915). Yet some of the muscle fibers of this diaphragmaticus connect with an aponeurosis that passes over the upper border of the liver and binds the liver to the esophagus (Reese, 1915). Whereas a contribution of the alligator diaphragmaticus to LES pressure seems unlikely, it cannot be ruled out. The amphibian diaphragm, which is not homologous to either the mammalian diaphragm or the crocodilian diaphragmaticus, originates on the pelvic girdle (the ilium) and inserts on the esophagus at the level of the LES. Contraction of the amphibian diaphragm increases LES pressure (Pickering et al., 2004; Pickering and Jones, 2002). Thus, further research is warranted to fully address the importance of the crocodilian diaphragmaticus to LES tone. Be that as it may, it is very clear from the data that the rise in LES pressure during ventilation is not due to thoraco-abdominal pressure fluctuations associated with ventilation. On the contrary, gastric (see Fig. 6) and proximal esophageal pressures decreased during bouts of ventilation compared with apnea.

(2) Long apneas are natural for alligators. Respiration in reptiles is characterized by intermittent bouts of ventilation and long periods of apnea (Hicks, 1998). In the study by Kiatchoosakun et al. (2002), consecutive hypoxia and hyperoxia induced apnea in only eight out of 12 piglets. The period of apnea was short (in the order of a few minutes) compared with the natural apneas occurring in alligators, which at room temperature can easily last for 20–30 min (C.G.F., personal observation).

(3) Alligators tolerate instrumentation extremely well, without the requirement of anesthesia, when instrumented through the oral cavity. It is desirable to avoid the use of anesthetics because they can interfere with smooth muscle tone and control. Furthermore, anesthetics can influence central nervous control of both ventilation and LES function.

(4) Alligators exhibit much greater magnitudes of response than mammals. While the maximum increase in LES tone during hyperventilation in piglets was 49%, we measured increases in LES pressure during bouts of ventilation of up to 3000% in the alligator.

Complex phenomena can often best be studied by a judicious choice of model organisms. For example, to study the regulation of capillaries, August Krogh, 1920 Nobel laureate in medicine, used the tongues of frogs, which are translucent and enabled him to make visual observations of small arteries, veins and capillaries. An understanding of evolution, excitable membranes and *hox* genes has benefited from the study of finches, squid giant axons and fruit flies, respectively. Gastroesophageal reflux disease is a complex phenomenon, with largely unknown etiology, but dysregulation of the lower esophageal sphincter may lie at the core of this common disease. Both humans and alligators share peristaltic-motor waves as a means of propelling foodstuffs distally and an LES that relaxes upon swallowing and prevents gastric acid from refluxing proximally. In addition, the clear relationship between ventilation and rise in LES pressure in both mammals and alligators indicates that reflexes exist to coordinate the gastrointestinal and pulmonary systems; however, this reflex is not yet fully understood in humans. The vastly greater magnitude of this reflex in alligators compared with mammals recommends them as a useful model system to study the regulation of LES function.

We are grateful to two anonymous reviewers for constructive criticisms of the manuscript, and to M. Heath for technical assistance. This research was supported by NSF IBN 0137988 to C.G.F. and a grant from S. Meyers.

References

Andrade, D. V., De Toledo, L. F., 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.

Busk, M., Overgaard, J., Hicks, J. W., Bennett, A. F. and Wang, T. (2000). Effects of feeding on arterial blood gases in the American Alligator, *Alligator mississippiensis*. *J. Exp. Biol.* **203**, 3117-3124.

Farmer, C. G. and Carrier, D. R. (2000a). Pelvic aspiration in the American alligator (*Alligator mississippiensis*). *J. Exp. Biol.* **203**, 1679-1687.

Farmer, C. G. and Carrier, D. R. (2000b). Ventilation and gas exchange during treadmill-locomotion in the American Alligator (*Alligator mississippiensis*). *J. Exp. Biol.* **203**, 1671-1678.

Gans, C. and Clark, B. (1976). Studies on ventilation of Caiman crocodilus (Crocodilia: Reptilia). *Res. Physiol.* **26**, 285-301.

Geyikoglu, F., Temelli, A. and Ozkaral, A. (2002). Muscle fiber types of the tunica muscularis externa at the upper part of the sparrow (Passer domesticus) esophagus. *Turk. J. Zool.* **26**, 217-221.

Harding, S. M. (1999). Nocturnal asthma: role of nocturnal gastroesophageal reflux. *Chronobiol. Int.* **16**, 641-662.

Hicks, J. W. (1998). Cardiac shunting in reptiles: mechanisms, regulation and physiological function. In *Biology of the Reptilia. The Visceral Organs*, Vol. G (ed. C. Gans and A. S. Gaunt). Ithaca, N.Y.: Society for the Study of Amphibians and Reptiles.

Ingelfinger, F. J. (1958). Esophageal motility. *Physiol. Rev.* **38**, 533-584.

Kiatchoosakun, P., Dreshaj, I. A., Abu-Shaweesh, J. M., Haxhiu, M. A. and Martin, R. J. (2002). Effects of hypoxia on respiratory neural output and lower esophageal sphincter pressure in piglets. *Pediatr. Res.* **52**, 50-55.

Mittal, R. K., Rochester, D. F. and McCallum, B. W. (1988). Electrical and mechanical activity in the human lower esophageal sphincter during diaphragmatic contraction. *J. Clin. Invest.* **81**, 1182-1189.

Mittal, R. K., Fisher, M., McCallum, R. W., Rochester, D. F., Dent, J. and Sluss, J. (1990). Human lower esophageal sphincter pressure response to increased intra-abdominal pressure. *Am. J. Physiol.* **258**, G624-G630.

Pennisi, E. (2003). Lean times, lean gut. *Science* **299**, 505.

Pickering, M. and Jones, J. F. X. (2002). The diaphragm: two physiological muscles in one. *J. Anat.* **201**, 305-312.

Pickering, M., Campion, D. and Jones, J. F. X. (2004). A gastrointestinal role for the amphibian 'diaphragm' of *Xenopus laevis*. *J. Zool.* **264**, 45-51.

Reese, A. M. (1915). *The Alligator and Its Allies.* New York: G. P. Putnam's Sons.

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. 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. (1998). A vertebrate model of extreme physiological regulation. *Nature* **396**, 659-662.

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.

Starck, J. M. (1999). Structural flexibility of the gastro-intestinal tract of vertebrates – implications for evolutionary morphology. *Zool. Anzeig.* **238**, 87-101.

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 Beese, K. (2002). Structural flexibility of the small intestine and liver of garter snakes in response to feeding and fasting. *J. Exp. Biol.* **205**, 1377-1388.

Starck, J. M., Moser, P., Werner, R. A. and Linke, P. (2004). Pythons metabolize prey to fuel the response to feeding. *Philos. Trans. R. Soc. London Ser. B* **271**, 903-908.

Theodoropoulos, D. S. and Ledford, D. K. (2000). Is GERD a factor in your patient's asthma?-gastroesophageal reflux disease. *J. Respir. Dis.* **21**, 238-252.

Yoshida, M. (2001). A light microscope study of the distribution of muscle in the frog esophagus and stomach. *J. Smooth Muscle Res.* **37**, 95-104.