

PERIPHERAL RECEPTORS AFFECTING BREATHING AND CARDIOVASCULAR FUNCTION IN NON-MAMMALIAN VERTEBRATES

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SUMMARY

Most vertebrates show respiratory and circulatory reflexes which can be traced to stimulation of various extero- or interoceptors. Widely distributed groups of exteroceptors, with a variety of stimulus modalities, are associated with defence reflexes which protect the respiratory passages and gas exchange surfaces. Other exteroceptors are associated only with the gas exchange surfaces. These are either mechanoreceptors or chemoreceptors and have a range of different dynamic characteristics, but are none-the-less amazingly uniform in their role in control of the normal breathing pattern. Intravascular receptors stimulated by the arterial blood pressure are located on all the gills in fishes, yet appear to be restricted to the pulmocutaneous arteries in anuran amphibians and to the truncal region or aortic root in reptiles and birds. On the other hand, the distribution of glomus-sustentacular-nerve cell complexes, associated with intravascular chemoreception, appears to be much more diffuse in higher than lower vertebrates. The wide distribution of these cell complexes may be attributed to their embryological origin from neural crest cells. Even so, the presence of these complexes does not appear to be essential for respiratory responses to environmental hypoxia since they have not been located in teleost fishes.

The role of peripheral receptors in controlling cardiovascular and respiratory functions, under steady state conditions in non-mammalian vertebrates, is not well defined and it may be that they are only modulators of circulatory and respiratory patterns arising from hormonal or humoral effects on the central nervous system.

INTRODUCTION

Many changes in the external or internal environments of vertebrates alter their cardiovascular and respiratory performance either directly, or indirectly by way of neural or endocrine intermediaries. Any adjustment in response to environmental changes is modulated in its expression by interaction with other control systems and by volitional, conditioned or habituation phenomena occurring within the central nervous system. The complexity of cardiovascular and respiratory control is outside the scope of this review which is restricted to a discussion of receptors which initiate, and perhaps maintain, neurally mediated reflexes. For convenience, we have divided these receptors into two groups, extero- and interoceptors, and their structure, loca-

tion, stimulus modalities and reflex effects are discussed. Exteroceptors are more diverse in their reflex effects and stimulus modalities than interoceptors, probably because they come into direct contact with the environment. Interoceptors, on the other hand, promote homeostasis and can be viewed as playing similar roles in all vertebrates. Despite such a broad approach we have tried to avoid the tendency to view the often discrete concentrations of receptors in higher vertebrates as the evolutionary apogee of more diffuse systems in fishes or amphibians. Such a phylogenetic view, while underlining homologies, would be simplistic and inaccurate.

(A) EXTERNAL RECEPTORS (*Exteroceptors*)

(1) *Receptors involved in defence reflexes*

A variety of sensory receptors provide vertebrates with information about many aspects of their environment. Although most of these receptors are involved in processes such as olfaction, taste, vision, and the detection of thermal and mechanical stimuli, they may also contribute, in varying degrees, to defensive reflexes which serve to protect the delicate gas exchange surfaces. Some receptors appear to serve this purpose exclusively.

As a consequence of low oxygen content and slow rate of oxygen diffusion in water, fish utilize a ventilatory system in which water flows continuously across the respiratory epithelium of the secondary lamellae of the gills. This water contains varying quantities of particulate matter in the form of suspended sediments, organic debris and microscopic flora and fauna, all of which may damage the lamellae or plug the openings of the inter-lamellar channels. Consequently, stimulating mechanoreceptors in the skin surrounding the pharynx, mouth, nostrils, spiracles and gill slits in the Port Jackson shark (*Heterodontus portusjacksoni*) produces a cough which flushes water backwards through the gills, an action well suited to removing obstructing particles (Satchell & Maddalena, 1972). Such reflex coughing occurs naturally in a variety of fish (Kuiper, 1907; Ballintijn, 1969; Holeton & Jones, 1975). Gulping and coughing may also be caused by stimulating rapidly adapting mechanoreceptors on the branchial processes and branchial pads of elasmobranchs (Satchell & Way, 1962) and the gill filaments of teleosts (Sutterlin & Saunders, 1969). These receptors are innervated by the IX and X cranial nerves, have receptive fields restricted to a single hemibranch and respond to mechanical displacement of the gill with a brief burst of high frequency discharge. There are also chemoreceptors in the orobranchial cavity of elasmobranchs which, in response to noxious chemical stimuli (ammonia or dilute acetic acid), elicit a cough in which the gill slits are closed and water is ejected through the mouth, preventing access to the gill lamellae (Satchell & Maddalena, 1972). Finally, receptors which appear to be nociceptors are also located on the gill filaments of elasmobranchs, innervated by the branchial branches of the X cranial nerve and with receptive fields extending from one to several gill filaments (Poole & Satchell, 1979). These receptors are stimulated by light touch, local oedema, phenyldiguanide and 5-hydroxytryptamine, and cause bradycardia, hypotension, and inhibition of ventilation and locomotion. It has been suggested that mechanical stimulation of these receptors may serve to inhibit not only breathing but also forward motion into water which contains parti-

ulate matter. The local oedema which can accompany exercise may also stimulate these receptors and initiate a reflex similar to the J reflex of mammals (Paintal, 1970) which prevents locomotion. The cessation of exercise is usually accompanied by a reduction in perfusion pressure which will alleviate the oedema.

In air breathers, receptors involved in defence reflexes are usually confined to the skin surrounding the nares and mouth and to the upper respiratory passages; their primary reflex effect is apnoea. In anurans (West & Jones, 1976), batrachians (Lombroso, 1913), and newts (Spurway & Haldane, 1953), all of these being aquatic or semi-aquatic amphibians, a water stimulus applied near the nares or mouth leads to apnoea. This response is elicited by mechanoreceptors whose sensory fibres are carried in the ophthalmic branch of the trigeminal (V cranial) nerve. Section of this nerve eliminates the response while stimulation of the cut central end causes narial closure and apnoea (West & Jones, 1976). There is some evidence to suggest that these receptors may adapt over the course of a few minutes (West & Jones, 1976). These receptors appear to function as the first line of defence against inhalation of water during submergence.

Zotterman (1949) found taste receptors on the tongue of the frog sensitive to the presence of water which may also be involved in defensive reflexes. These 'water receptors' are innervated by large sensory fibres carried in the glossopharyngeal nerve and their stimulation leads to reflex closure of the mouth, and apnoea. Although water does not normally enter the mouth on submergence, if some were to do so, this reflex could be important as a second line of defence, by reducing buccal volume and expelling water from the buccal cavity (West & Jones, 1976).

A similar back-up mechanism appears to exist in birds, particularly diving birds. A variety of receptors have been found, located on the bill, tongue, glottis and internal respiratory passages innervated by the trigeminal, glossopharyngeal, vagus and hypoglossal nerves (Graham, 1940; Andersen, 1963; Jones & Purves, 1970*a*; Gregory, 1973; Leitner & Roumy, 1974*a, b*; Bamford & Jones, 1974). Their stimulation invariably inhibits inspiration (Huxley, 1913*a, b*; Graham, 1940; Butler & Jones, 1968; Eaton, Fedde & Burger, 1971) and may enhance expiratory intercostal muscle activity (Leitner, Koumy & Miller, 1974). The receptors vary in type from mechanoreceptors with varying degrees of thermal sensitivity on the bill (Gregory, 1973; Leitner & Roumy, 1974*a, b*) to some strictly thermo-sensitive receptors on the glottis (Bamford & Jones, 1974), and 'water-receptors' on the tongue (Kitchell, Ström & Zotterman, 1959). It would appear that under natural conditions, in diving birds as in the frog, reflex inhibition of breathing is initiated by receptors in the nares but that receptors from the tongue and glottis will contribute to the apnoea if stimulated. Also, in such diving birds as ducks, swans and cormorants, there is evidence that mechanoreceptors associated with the cervical musculature and labyrinths induce a 'postural apnoea' on straightening the neck or dorsiflexion of the head on the neck (Huxley, 1913*b*; Paton 1913, 1927; Koppányi & Kleitman, 1927), further contributing to the apnoea accompanying submergence.

Smyth (1939) suggested that there were CO₂ receptors in the larynx or around the glottis in frogs which also cause apnoea when stimulated. This has not been confirmed by recent work, which shows that external CO₂ sensitive receptors exist but are located

on the skin and nasal mucosa (Sakakibara & Akiyama, 1977; Sakakibara, 1978). These receptors respond well to high levels of CO_2 in air and a few may be sensitive to levels as low as 0.5%. Sectioning of olfactory and trigeminal nerves abolishes the apnoeic response. Although stimulation leads to respiratory inhibition, the high levels of CO_2 required and the delay of 4–8 s between stimulus and response indicate that this response is akin to a nociceptive response to noxious stimuli rather than part of a breath-by-breath control system. Similar CO_2 sensitive chemoreceptors have been located on the palate of fish (carp) innervated by palatine, facial and branchial nerves and are believed to be modified taste buds (Konishi *et al.* 1969; Hidaka, 1970). Although the reflex effects of stimulating these receptors are unknown, behavioural studies indicate that free-swimming fish show strong preference responses to the lowest levels of CO_2 and pH when exposed to external gradients in CO_2 and pH (Shelford & Allee, 1913; Scharrer, Smith & Palay, 1947; Höglund, 1961).

Unlike amphibians, most aquatic reptiles continue pumping movements of the hyoid to draw water in and out of the mouth on submergence, primarily for olfactory purposes (Mitchell & Morehouse, 1863; McCutcheon, 1943; Naifeh, Huggins & Hoff, 1970). Defence reflexes to terminate ventilation on submergence still exist, however. Mechanoreceptors in the posterior nares, larynx and glottis all terminate ventilation on stimulation and also induce pulmonary vasoconstrictor reflexes (reflex lung contraction and pulmonary artery constriction, Carlson & Luckhardt, 1920). Therefore, receptors which are part of the second line of defence in amphibians are now most important in eliciting an apnoeic response to submersion but which is independent of closure of the mouth and nares. The lungs remain protected while the mouth is freed for other activities.

(2) *Receptors involved in control of the breathing pattern*

Despite the anatomical variations found in gas exchange organs, all of the vertebrates have exteroceptors, in the form of mechano- and/or chemoreceptors, located in the lower respiratory passages and the gas exchange organs. These receptors primarily convey information about the rate and amplitude of the ventilatory effort and contribute to reflexes ensuring an efficient breathing pattern and proper ventilation-perfusion matching at the gas exchange surface. The latter is achieved through reflex effects on heart rate, cardiac output, arterial blood pressure and even blood flow distribution, via intracardiac shunting, in those species with incompletely divided hearts. Furthermore, during ventilation, these reflexes regulate the lung tonus established by the extensive pulmonary smooth muscle network of many of the lower vertebrates.

Both elasmobranch and teleost fishes have proprioceptors associated with the internal openings of the gills, innervated by the post-trematic branches of cranial nerves IX and X (Satchell & Way, 1962, Sutterlin & Saunders, 1969). Although little has been reported concerning the discharge characteristics of these receptors in teleosts, they have been well characterized in elasmobranchs, where these receptors are known to have a medium to high threshold for stimulation and exhibit both static and dynamic responses to displacement of the branchial processes. Some receptors show only dynamic responses adapting completely to a sustained deflexion, and many also show

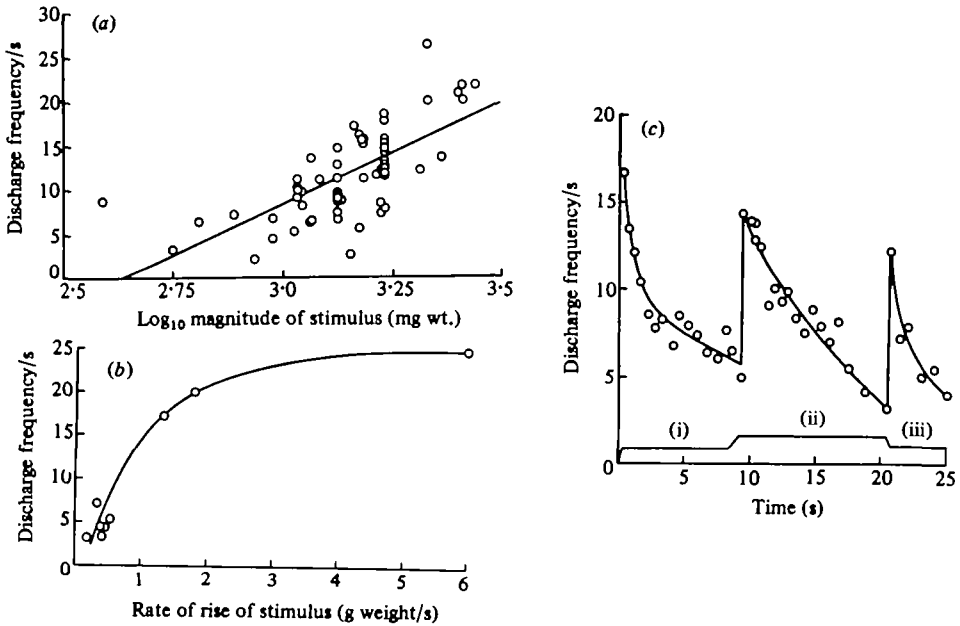


Fig. 1. The relation of discharge frequency from a branchial mechanoreceptor in the dogfish, *Squalus acanthias*, to (a) stimulus amplitude and (b) rate of onset of the stimulus in the dogfish. (c) Discharge of a mechanoreceptor in response to deflexions of a branchial process. The lower line shows the pattern of deflexion: (i), 189 mg.wt.; (ii), 333 mg.wt.; (iii), 222 mg.wt. (from Satchell & Way, 1962).

another burst of activity when the process is returned to its normal position (Fig. 1c). Consequently, this dynamic discharge is proportional to the rate of deflexion (Fig. 1b; Satchell & Way, 1962). Others produce a continuous discharge during deflexion which is proportional to the amplitude of deflexion (Fig. 1a). During normal ventilation, peak discharge occurs during peak branchial cavity contraction (Satchell, 1959). As pointed out by Satchell & Way (1962) these receptors may signal pharyngeal movements associated with the expulsive phase of the respiratory cycle as well as maintained displacement during fast forward swimming.

In elasmobranchs, the dynamic component of receptor discharge appears to have the strongest effect on ventilation and leads to a breath-by-breath regulation of breathing frequency. The duration of inspiration and the pause which normally precedes the next expiration (Hughes, 1960*a, b*) are proportional to the amplitude of deflexion of the branchial processes during the preceding expulsive phase of the respiratory cycle. That is, increased respiratory amplitude produces an increased dynamic component to the receptor discharge which reflexly slows breathing frequency (Satchell & Way, 1962). The amplitude of each branchial contraction is inversely related to the branchial volume or flow rate of water through the branchial chamber (Satchell, 1961). That is, with increasing water flow rates due to swimming, there is increased displacement of the branchial processes and an increased level of static discharge from the receptors which leads to a reduction in the breathing effort. With

ventilation volume and breathing frequency inversely related in this fashion, any increase in branchial volume (therefore, increased static discharge) which resulted in a decreased ventilation volume (and therefore, a decreased dynamic signal) would also result in an increased breathing frequency maintaining an adequate level of minute ventilation. It does not appear necessary to postulate separate receptors for ventilation volume and frequency responses to changes in gill water flow (Satchell, 1959; Satchell & Way, 1962), but merely separate central integration of dynamic and static discharge profiles arising from a single group of receptors.

In teleosts, the magnitude of the inspiratory effect is also inversely related to branchial volume or rate of water flow through the branchial chamber (Lutz, 1930; Ogden, 1945) leading to a breath-by-breath regulation of ventilation volume (not frequency as in elasmobranchs) implying a stronger influence on ventilation from the static component of the receptor discharge.

These receptors also appear to control the switch from active to ram ventilation in those fishes utilizing this form of ventilation at high swimming speed (Roberts, 1975; Freadman, 1981). It has further been shown that discharge from these receptors reflexly alters tonic vagal activity to the heart (Lutz, 1930; Satchell, 1960, 1968; Taylor & Butler, 1981) which could result in a change in heart rate in synchrony with branchial contraction. Although this appears to hold for teleosts, a direct and consistent phasing relationship in cardio-respiratory coupling has not always been found in elasmobranchs (Taylor & Butler, 1971; Hughes, 1972).

In the lunged fishes, amphibians and reptiles, the respiratory passages are generally short and the lungs usually consist of bag-shaped sacs with several septa containing strands of smooth muscle. These septa subdivide each lung into a series of chambers. Each chamber opens directly off the primary bronchus and is partially subdivided by further septa into smaller subdivisions of the cavity, frequently referred to as alveoli (Fig. 2a; Gaupp, 1904; Wolf, 1933; Marcus, 1937).

Although indirect evidence suggests the lungs of lungfish contain pulmonary stretch receptors, nothing is known of their location, innervation or discharge characteristics. In anuran amphibians, pulmonary stretch receptors are located in subepithelial connective tissue in the pulmonary walls and septa. They are more densely distributed near the bronchus and are described as free endings (terminal clews, or needle or plaque shaped endings, Cuccati, 1888; Gaupp, 1904). The primary location and distribution of pulmonary stretch receptors in the turtle lung also follows this pattern (Fig. 2b; Milsom & Jones, 1976; Jones & Milsom, 1979).

Many investigators have recorded from these receptors in frogs over the years (Carlson & Luckhardt, 1920; Neil, Ström & Zotterman, 1950; Bonhoeffer & Kolat, 1958; Taglietti & Casella, 1966; McKean, 1969) and, on the basis of their discharge characteristics, these receptors can be divided into three groups. Proportional sensitive receptors, responding only to the degree of lung inflation, make up 20% of the population of pulmonary stretch receptors. Rate sensitive receptors, which respond only to the dynamic phase of change in lung volume, constitute a further 30% of the population; and the remaining 50% is composed of receptors which are both proportional and rate sensitive (McKean, 1969; Milsom & Jones, 1977). This latter group shows varying degrees of rate and proportional sensitivity from almost pure pro-

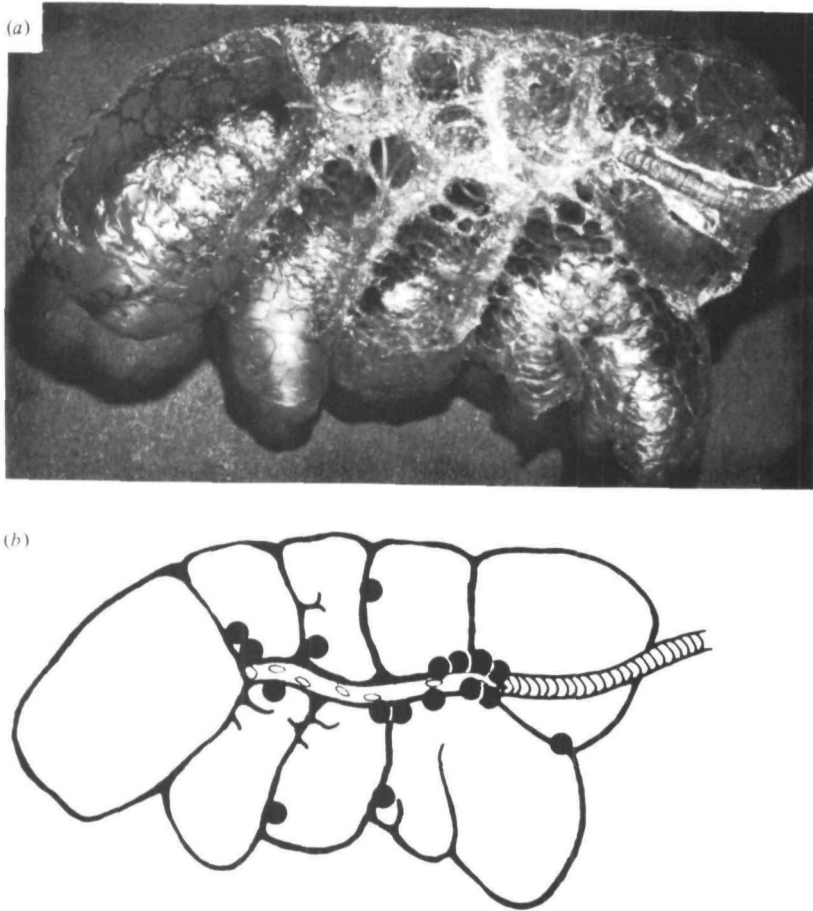


Fig. 2. (a) Dry mount of the left lung of the turtle, *Chrysemys picta* showing internal septation. (b) Schematic diagram of left lung showing approximate location of 17 pulmonary receptors (●) located by punctate stimulation.

portional sensitive receptors, with minimum rate sensitivity, to almost pure rate sensitive receptors with minimum proportional sensitivity. In all three groups, discharge frequency shows a complex relation to both lung volume and pulmonary pressure changes during lung inflation (Fig. 3*a*), but is linearly related to the 'calculated' wall tension of the pulmonary wall which is a function of both volume and pulmonary pressure (Fig. 3*a*). $\Delta\text{tension} = \int_{V_0}^{V_1} PdV/\Delta S$; where V = lung volume, P = transpulmonary pressure, and ΔS is the increase in surface area when the lung expands from V_0 to V_1 (Taglietti & Casella, 1966; McKean, 1969).

McKean (1969) has suggested that the various response characteristics of all three groups could be accounted for by a single type of nerve ending, depending on its location within the lung. Thus, the proportional response is a response to lung stretch as well as to stress adaptation phenomena, i.e. to the mechanical properties of the lung as a whole. The rate response is due to regional differences in the mechanical properties of the lung. Since there are no conducting airways within the lung, the rate response cannot be due to flow resistance within the airways and must be due to tissue viscosity or regional differences in the viscosity to elasticity ratio (a large ratio would produce a small rate response, a low ratio would produce a large rate response).

Lung deflation receptors have also been reported in the lungs of frogs. These receptors increase discharge when the lung is deflated from a maintained inflation to normal resting lung volume (Taglietti & Casella, 1968). Taglietti & Casella (1968) claimed that the discharge of a population of pulmonary receptors demonstrated a better correlation with the mechanical state of the lung than single unit recordings and so they extracted their information from multi-unit recordings. As a consequence, it is impossible to determine whether these receptors respond only to deflation from maintained inflation or whether they are rate sensitive receptors which respond to lung volume changes in either direction. Thus, it is unclear whether these receptors are anything more than the conventional type of pulmonary stretch receptor.

Slowly adapting pulmonary stretch receptors in turtles appear to constitute a uniform population and show both static and dynamic responses to lung inflation. The dynamic, rate dependent responses, however, only occur with large inflation volumes. All responses differ only quantitatively from those of bronchopulmonary stretch receptors in mammals. The lower discharge frequencies, pressure sensitivity and conduction velocity are probably due to the lower body temperatures of turtles (Milsom & Jones, 1976; Jones & Milsom, 1979). Available evidence suggests this is also true for the pulmonary stretch receptors of lizards (Fedde, Kuhlmann & Scheid, 1977; Scheid, Kuhlmann & Fedde, 1977).

In turtles, stretch receptor discharge follows changes in lung volume almost exactly indicating that volume is the major stimulus modality (Fig. 3*b*). During pump ventilation of the lungs, both discharge and volume lag behind the changes in transpulmonary pressure (Fig. 3*b*; Jones & Milsom, 1979). This is not surprising since these receptors are located on the internal septa subdividing the major lung chambers and do not experience changes in transpulmonary pressure. Internal septa are exposed to the same pressure and flow changes on each side during ventilation (Fig. 2). The response of these receptors to rate of inflation, recorded at high inflation volumes, may

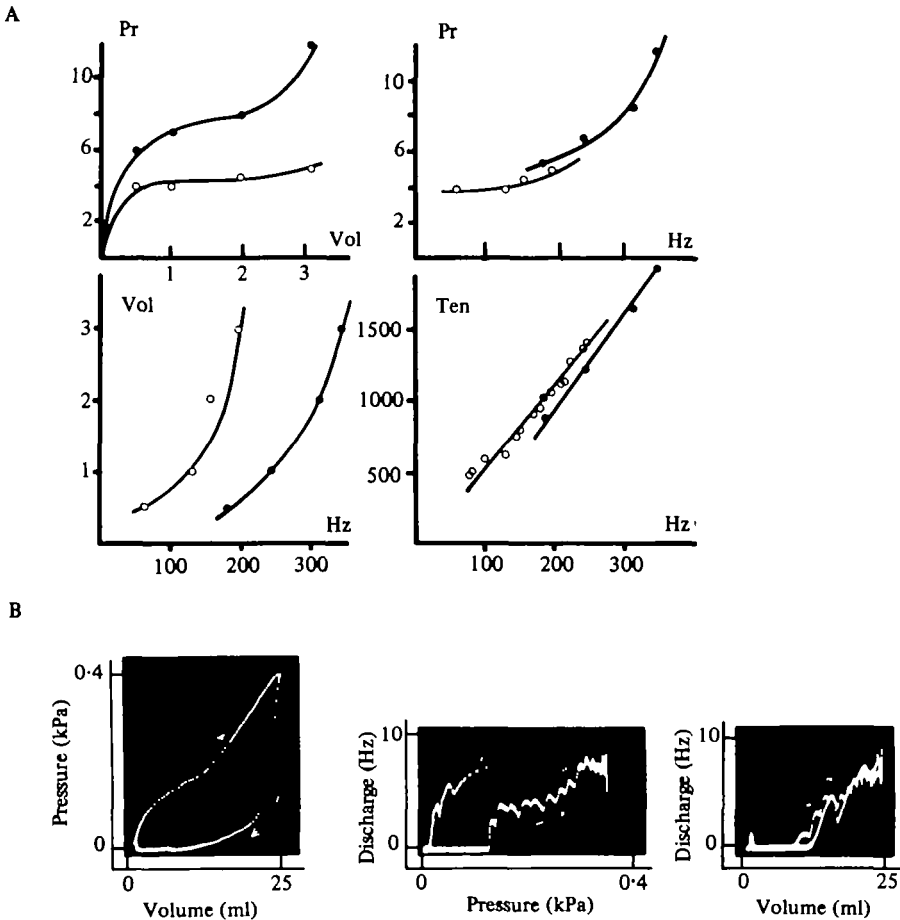


Fig. 3. (A) Pressure-volume diagram of the lung of a frog taken from data during the first 10 s (●) and last 10 s (○) of a one minute inflation as well as receptor discharge plotted as a function of volume (Vol., ml), pressure (Pr, g/cm²) and tension (Ten, erg/cm²) at both these times (adapted from Taglietti & Casella, 1966). (B) Pressure-volume diagram of the lung of the turtle, *Chrysemys picta*, during a single ventilation cycle as well as plots of receptor discharge versus inflation pressure and inflation volume during the same cycle (from Jones & Milsom, 1979).

arise from transient changes in the longitudinal tension of the septa during inflation at high air flow rates (Jones & Milsom, 1979), i.e. changes due to the tissue viscosity to elasticity ratio as suggested by McKean (1969) for receptors in the frog lung.

Although pulmonary stretch receptors have been found in the lungs of birds, with sensory fibres carried in the vagus nerve, their structure, location and discharge characteristics are poorly known. Approximately 50% of vagal fibres exhibiting respiratory modulation in the chicken (Fedde & Petersen, 1970; Leitner, 1972; Molony, 1972, 1974) and 20% in the duck (Fedde *et al.*, 1974*a, b*; Leitner & Roumy, 1974*c*) are stimulated by either inflation or deflation. During spontaneous breathing most receptors start firing immediately on inspiration, increase discharge with deeper breaths, and stop firing close to peak inspiration. The firing patterns of many of these

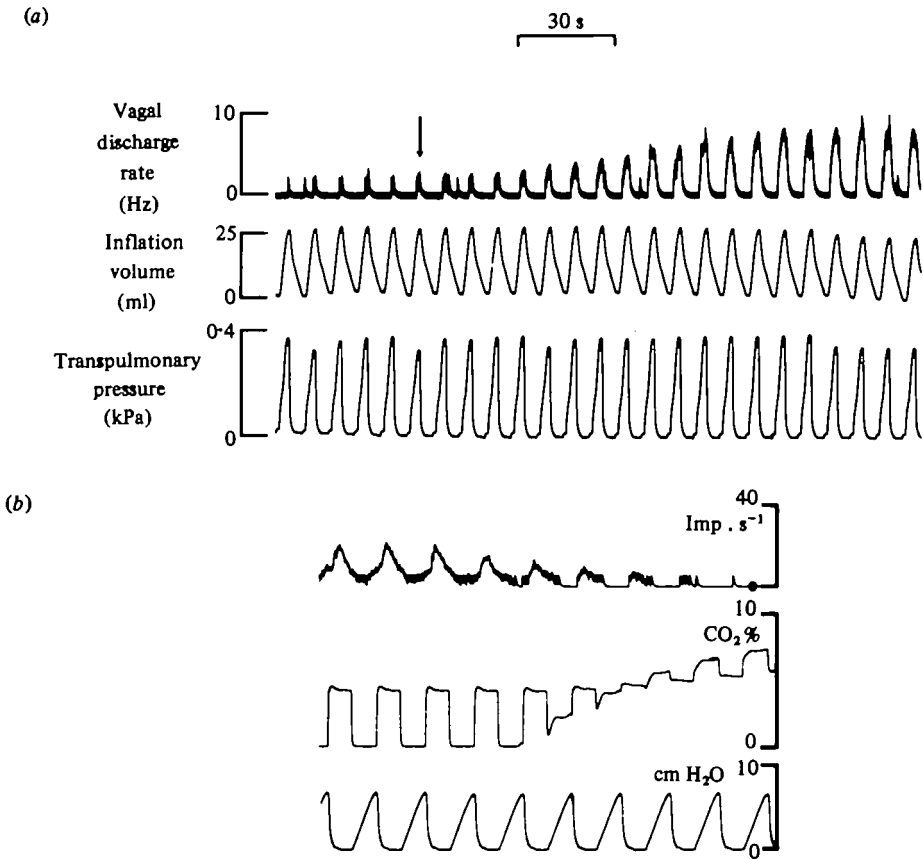


Fig. 4. (a) Effect of changing airway CO_2 concentration on discharge from a pulmonary stretch receptor in the turtle *Chrysemys picta*. 10% CO_2 was removed from the ventilating gas at the arrow (\downarrow) (from Milsom, unpublished). (b) Effect of changing airway CO_2 concentration on discharge from a single intrapulmonary CO_2 receptor in the muscovy duck, *Cairina moschata*. Upper trace shows discharge frequency, middle trace, airway CO_2 concentration and lower trace, pulmonary pressure (from Fedde *et al.* 1974).

mechanoreceptors suggest that they are located not in the lungs but in the lower respiratory tract, in the thoracic septa, or in other associated membranes of the thoraco-abdominal cavity (see Bouverot, 1978, for review).

Besides their mechanosensitivity, the pulmonary stretch receptors of frogs, turtles and lizards also show varying degrees of chemosensitivity in that their discharge is inhibited by increasing levels of CO_2 (Milsom & Jones, 1976, 1977; Fedde *et al.* 1977; Scheid *et al.* 1977; Jones & Milsom, 1979; Kuhlmann & Fedde, 1979). Some fibres show little inhibition by CO_2 while others are extremely sensitive, being totally inhibited by levels of 1–5% CO_2 in the inspired gas (Fig. 4a). Thus, there is a tremendous polymodal distribution of CO_2 sensitivity in the receptor population. On average, receptor discharge in both frogs and turtles is about 50% reduced in response to lung inflation with 10% CO_2 in air ($F_{I,\text{CO}_2} = 10\%$; Milsom & Jones, 1977; Jones & Milsom, 1979) while in lizards discharge is 50% reduced by only 4–8% CO_2

(Fedde *et al.* 1977). This CO₂ sensitivity is enhanced in frogs and turtles by increasing the volume of lung inflation (Jones & Milsom, 1979; Kuhlmann & Fedde, 1979), but not in lizards (Fedde *et al.* 1977).

Neuroepithelial bodies have been found in the lungs of urodeles (Goniakowska-Witalinska, 1980) and anuran amphibians (Rogers & Haller, 1978; Wasano & Yamamoto, 1978). These have the properties to act as chemoreceptors sensitive to oxygen and/or CO₂ in the inhaled air, but attempts to record from nerve fibres arising from pure chemoreceptors in the lungs of amphibians and turtles have been unsuccessful (Milsom & Jones, 1977; Kuhlmann & Fedde, 1979; Jones & Milsom, 1979).

Circumstantial evidence has been presented for the presence of airway CO₂-sensitive receptors in the green turtle (Jackson & Prange, 1977). These animals increase respiratory frequency on the first breath following an F_{I,CO_2} increase to 6% and resume normal breathing on the first breath of room air. This response is much quicker than that reported for CO₂-sensitive pulmonary stretch receptors in freshwater turtles (Fig. 4a; Jones & Milsom, 1979) but does not definitively preclude a role of CO₂-sensitive pulmonary stretch receptors, lung chemoreceptors or airway irritant receptors (6% F_{I,CO_2} may be a noxious stimulus) in this species.

Pure chemoreceptors have, however, been demonstrated in the lungs of lizards and birds. Although their location in lizards is poorly defined (Scheid *et al.* 1977), in birds they are primarily located within the parabronchi although there is no strong agreement on their longitudinal distribution (Osborne & Burger 1974; Burger, Osborne & Banzett, 1974; Powell *et al.* 1978). Physiological studies indicate that avian receptors are either distributed symmetrically between the peripheral and luminal sides of the mantle or are located in the epithelial lining of the parabronchial lumen (Crank, Kuhlmann & Fedde, 1980).

King *et al.* (1974) have described sensory structures in this region of the avian lung consisting of (1), granular cells, associated with afferent axons, in the epithelium around the orifices of the craniomedial secondary bronchi, (interpreted as a neurite-receptor cell complex) and (2), axonal endings in the basal regions of the epithelium of the primary and secondary bronchi, in the bronchial smooth muscle and under the atrial epithelium. The second group are of the free and encapsulated type of endings previously described by McLelland (1972, 1973). It is postulated that the most likely candidate to fit the required characteristics of the pulmonary chemoreceptors is the granular cell complex which has characteristics similar to merkel cells and carotid body glomus cells (King *et al.* 1974).

The sensory nerves from these receptors are carried in the vagus in lizards (Fedde *et al.* 1977) and both vagal and cardiac sympathetic nerves in birds (Burger *et al.* 1974). Their activity appears to be inversely related to the CO₂ concentration of pulmonary gas, static discharge frequencies being maximal when the lungs are exposed to air and decreasing curvilinearly in response to increasing F_{I,CO_2} (Fedde & Petersen, 1970; Leitner, 1972; Fedde *et al.* 1974a,b; Leitner & Roumy, 1974c; Osborne & Burger, 1974; Molony, 1974; Molony, Graf & Scheid, 1976; Burger *et al.* 1976; Fedde *et al.* 1977; Scheid *et al.* 1977). Activity is totally inhibited at mean values of F_{I,CO_2} of 2% in the lizard (Fedde *et al.* 1977), 5% in the chicken and emu (Osborne & Burger, 1974; Burger *et al.* 1978), and 10% in the duck (Fedde *et al.* 1974a). Most fibres are

insensitive to stretch, at least for pressure excursions between 2 and 20 torr in birds and 8 to 20 torr in lizards (Fedde *et al.* 1974*a, b*; Fedde *et al.* 1977). In birds, receptor activity can be modified when P_{CO_2} at receptor sites is altered by changing CO_2 in the ventilating gas, in the pulmonary arterial blood or by changing ventilatory flow rates or perfusion rates (Molony 1974; Burger *et al.* 1974; Banzett & Burger, 1977; Powell, Barker & Burger, 1980). These receptors do not respond to hypoxia, hyperoxia or sodium cyanide in either lizards or birds (Fedde & Petersen, 1970; Burger *et al.* 1974; Scheid *et al.* 1977), their response to pH is equivocal (Burger *et al.* 1974; Scheid *et al.* 1977; Powell *et al.* 1978) and in birds, they are inhibited by veratridine and volatile anaesthetics (Fedde & Petersen, 1970; Molony, 1974).

Several lines of evidence support the idea that these receptors are specific CO_2 receptors and not CO_2 -sensitive mechanoreceptors. (1) When CO_2 is suddenly removed from the ventilating gas stream under unidirectional ventilation there is a burst of neural activity (overshoot) from pulmonary chemoreceptors which then diminishes to the steady state values for the new gas composition. Conversely, when CO_2 is added to the gas stream there is an onset transient (undershoot) before discharge returns to the new, lower steady state level for that particular gas composition (Molony, 1974; Osborne *et al.* 1977*a*; Fedde *et al.* 1977). (2) Some individual CO_2 -sensitive vagal afferents can respond rhythmically to sinusoidal changes in CO_2 up to 2.7 Hz in birds (Osborne, Burger & Stoll, 1977*a*), and 0.64 Hz in lizards (Fedde *et al.* 1977). Pulmonary mechanoreceptors do not exhibit these dynamic characteristics. (3) During spontaneous breathing, mechanoreceptors start firing immediately on inspiration, peak discharge occurs close to peak inspiration, and discharge increases with deeper breaths. The pattern is unaffected by altering upper respiratory dead space. Chemoreceptors, during spontaneous ventilation (chicken, duck & dove), begin firing with a delay of about 0.35 s after inspiration begins, peak discharge may occur during inspiration, expiration, or during both phases of the ventilatory cycle, and the delay following onset of inspiration is prolonged by increasing upper respiratory dead space (King *et al.* 1968*a-c*; Jones, 1969; Fedde & Petersen, 1970; Molony, 1974).

Despite the differences in stimulus modality between the pulmonary stretch receptors and pulmonary chemoreceptors found in various animal groups, all evidence indicates that all pulmonary receptors have the same functions and elicit the same responses (Milsom & Jones, 1980). Thus, the intrapulmonary chemoreceptors in birds and presumably lizards are the sensory limb of an inspiratory-inhibitory reflex which uses the rate and extent of CO_2 washout during inspiration as the sensory signal rather than the rate and extent of lung expansion monitored by pulmonary stretch receptors (Burger *et al.* 1974; Fedde *et al.* 1974*a, b*; Molony, 1974; Banzett & Burger, 1977; Burger *et al.* 1978; Milsom, Jones, & Gabbott, 1981). As such, they make an important contribution to regulation of the breathing pattern. They do not, however contribute in any significant way to specific ventilatory responses to increased metabolic CO_2 production which would act to maintain arterial P_{CO_2} homeostasis (Milsom *et al.* 1981) as has been suggested by many authors (Banzett & Burger, 1977; Osborne & Mitchell, 1977; Osborne, Mitchell & Powell, 1977*b*; Powell *et al.* 1978; Scheid *et al.* 1978; Mitchell & Osborne, 1979).

The consistency in function found in all receptor groups, regardless of primary

stimulus modality, suggests that a pulmonary receptor with both distinct mechano- and chemosensitive properties may represent the functional precursor of the more specialized pulmonary receptor types which have evolved in birds and mammals (Milsom & Jones, 1976, 1977; Fedde & Kuhlmann, 1978). Consequently, CO₂ receptors predominate in the relatively inexpandible, constant-volume avian lung, while mechanoreceptors with only a low sensitivity to CO₂ are found in the expandible but relatively hypercarbic lungs of mammals. Each group of vertebrates has apparently utilized the most convenient sensory modality for monitoring the rate and extent of each ventilatory effort.

(B) INTERNAL RECEPTORS (*Interoceptors*)

(1) *Intravascular chemoreceptors*

In vertebrates, the tissue associated with intravascular chemoreception has a characteristic association of glomus cells (also known as chief cells or Type I cells), sustentacular cells (also known as Type II cells) and nerve terminals (Fig. 5). The evidence implicating this association of nerves and cells in chemoreception is only circumstantial but, as H. D. Thoreau pointed out in 1850, 'some circumstantial evidence is very strong, as when you find a trout in the milk'. A number of glomus cells are usually associated together and these may be in electrical or chemical synaptic contact (Fig. 5; Ishii & Ishii, 1976). Isolated cells have been observed in amphibians, reptiles and birds (Kobayashi, 1969, 1971 *a, b*), however, in lower vertebrates, glomus cells are usually in small groups separated from each other by connective tissue (Kobayashi, 1975). This is quite unlike their arrangement in mammals (McDonald, 1981). The fine blood vessels which supply the chemoreceptive elements have occasionally been described as 'sinusoids' (Adams, 1958; Rogers, 1966; Fu & Tcheng, 1966; Ishii & Oosaki, 1969) although most are 'fenestrated', that is, the endothelial cells have small holes closed by a thin diaphragm (Fig. 5; Hodges *et al.* 1975). These blood vessels have a rich adrenergic innervation (sympathetic) and probably also some innervation from the parasympathetic branch of the autonomic nervous system (Pouillet-Krieger, 1973).

Glomus cells are large epithelial cells (5–10 μm in diameter) and frequently have long processes which come extremely close (0.3–0.5 μm) to blood capillaries (Butler & Osborne, 1975; Hodges *et al.* 1975). The cell nucleus is large, spherical or ovoid, and has a prominent nucleolus (Fig. 5). A characteristic feature of glomus cells is the presence of large, electron-dense, cytoplasmic vesicles, 0.1–0.2 μm in diameter, which probably contain polypeptides in addition to catecholamines. In amphibians, these vesicles have been described as 'budding' off the Golgi complex (Ishii & Oosaki, 1969). The profusion of these vesicles and other cytoplasmic organelles such as ribosomes, endoplasmic reticulum, and mitochondria suggests that glomus cells have an endocrine function.

Nerve endings, varying in shape from boutons to calyces, are in synaptic contact with glomus cells. At efferent synapses (nerve to glomus cell) the glomus cell membrane is thickened and clear vesicles, bounded by the axonal membrane, accumulate opposite the thickening of the glomus cell membrane (Fig. 5). Purely efferent synapses have

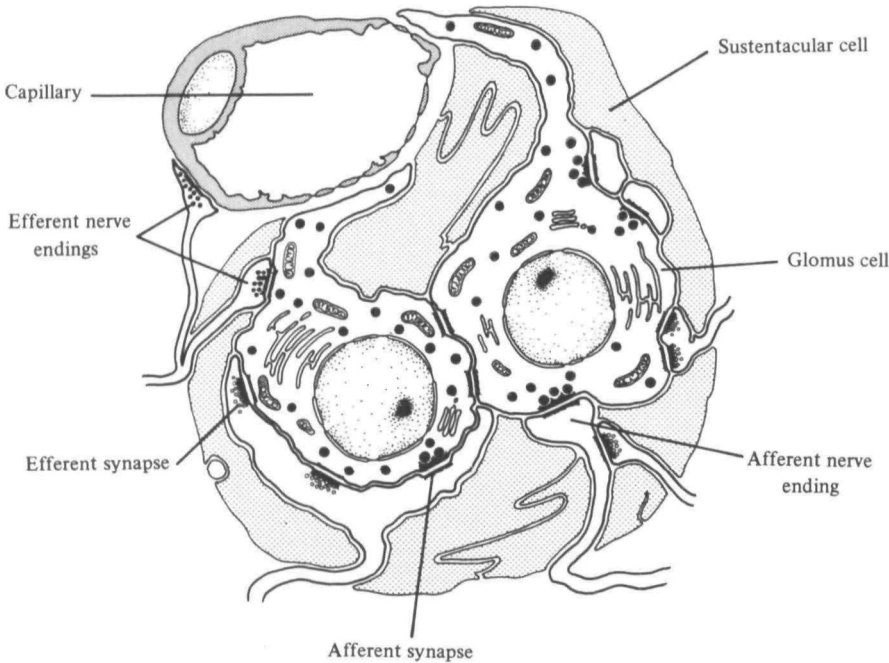


Fig. 5. Diagrammatic representation of the presumed chemoreceptive unit in vertebrates, composed of glomus cells, sustentacular cells, and both afferent and efferent nerve endings. The calyx type nerve ending makes reciprocal synaptic contact with the glomus cell. Sympathetic efferent nerves are shown innervating both a glomus cell and a fenestrated capillary.

been described in amphibians and birds (Thomas, Baretz & Krieger-Poulet, 1970; King *et al.* 1975; Ishii & Ishii, 1976). Afferent synapses (glomus cell-to-nerve), between glomus cells and sensory nerves, are characterized by an accumulation of electron-dense vesicles at the pre-synaptic (glomus cell) membrane. In some studies these vesicles appear identical to those which characterize the glomus cells (Ishii & Oosaki, 1969; Poulet-Krieger, 1973; Butler & Osborne, 1975) while in others they are smaller ($0.03\text{--}0.1\ \mu\text{m}$ in diameter) and only the central core of the vesicle is electron-dense (Kobayashi, 1971*b*; King *et al.* 1975). It is probable that the majority of glomus cells in amphibians and birds are innervated only by sensory nerves (Poulet-Krieger, 1973; Butler & Osborne, 1975). Also, chalice-like nerve endings may nearly envelope the glomus cell and, in both amphibians and birds, these nerve endings are in reciprocal synaptic contact with the glomus cells (Fig. 5; Butler & Osborne, 1975; King *et al.* 1975; Yamauchi, 1977). Hence, these nerve connexions are both afferent and efferent and have a similar distribution of vesicles and asymmetrical membrane thickenings as described for purely afferent and efferent terminations. One sensory nerve probably innervates a number of glomus cells so there is the possibility of efferent modulation of glomus cell activity (Ishii & Ishii, 1970) through reciprocal synaptic connexions, both at the level of a single glomus cell and between glomus cells sharing a single axon. Nerve:nerve synapses (Butler & Osborne, 1975), however, as well as a sympathetic efferent innervation (Fig. 5; Ishii & Ishii, 1976) could also be expected to modulate chemoreceptor discharge.

The glomus cells and their associated nerves are invested by sustentacular cells. Glomus cells usually outnumber sustentacular cells in most aggregations of chemo-receptive tissue. In their ultrastructural characteristics, the sustentacular cells resemble Schwann cells and their function is literally sustentacular (Kobayashi, 1971*b*).

Besides polypeptides (enkephalins?), glomus cells contain catecholamines or indole amines (Kobayashi, 1971*a*). In the chicken (*Gallus domesticus*) the important amine is 5-hydroxytryptamine, whereas in Japanese quail (*Coturnix coturnix japonica*), it is dopamine, although some nor-adrenaline may also be present (Pearse *et al.* 1973). In anuran amphibians the important transmitter may be dopamine (Ishii & Ishii, 1967) although adrenaline and nor-adrenaline are also present in chemoreceptive tissue (Banister, Portig & Vogt, 1967; Pouillet-Krieger, 1973).

Glomus cells closely resemble other polypeptide secreting cells in the body in both the nature of their cytoplasmic inclusions and ultrastructural characteristics. Pearse (1969) suggested that, on the basis of their ability to take up and decarboxylate amines and their precursors, glomus cells could be classified as members of the APUD series (*Amine Precursor Uptake and Decarboxylation*). All APUD cells produce peptides and/or amines as hormones or neurotransmitters and are all derived from neuro-endocrine-programmed cells originating in the embryonic ectoblast (Pearse & Polak, 1978). Avian glomus cells (in common with adrenal medullary and calcitonin producing cells of the ultimobranchial gland) are derived from cells of the rhombencephalic neural crest (Le Douarin, Le Lièvre & Fontaine, 1972; Pearse *et al.* 1973; Le Lièvre & Le Douarin, 1975; Le Douarin, 1978). These neural crest cells also give rise to the arterial walls of the major central blood vessels (except the endothelium). Obviously a major property of neural crest cells is their ability to migrate and, although local conditions may contribute to the pattern of differentiation, many cells appear to be pre-programmed. Consequently, it is not really surprising that knots of glomus-type cells should be spread somewhat diffusely throughout the central cardiovascular area (Fig. 6; Muratori, 1962). An affinity between these diverse cell groups has long been recognized on the basis of their chromaffinity (Stilling, 1898; Köse, 1902) and the term 'paraganglia' is most often used to describe them (Kohn, 1900). Some of these 'paraganglia', however, apparently lack innervation and some show different ultrastructural (Abdel-Magied, 1978*a*) and staining characteristics from glomus cells (Bennett, 1971*a, b*). Nevertheless, taking the broadest view, perhaps even the neurite-epithelioid cell complexes in the lung (see above) could be regarded as part of a common diffuse chemoreceptive system (de Kock, 1958, 1959).

In anuran amphibians, glomus cells are sparsely distributed among the *pars capillaris* region of the carotid labyrinth, a complex vascular structure at the division of the common carotid into external and internal carotid arteries (Kobayashi & Murakami, 1975; Smith *et al.* 1981*b*). Although functions such as regulation of blood flow have been proposed for the labyrinth (Carman, 1955; Banister, Herpol & Nail, 1975; Noguchi & Kobayashi, 1977; Smith *et al.* 1981*b*) there can be no doubt of its chemo-receptive function. It is the singular most important structure in anurans for initiating hyperpnoea in response to oxygen lack (Smyth, 1939). Action potential frequency in the IX nerve increases when the carotid labyrinth of the toad (*Bufo vulgaris*) is perfused with N₂-equilibrated saline, 2% NaCl solution or weak solutions of cyanide and this

increase in nerve activity corresponds with a stimulation of breathing (Ishii, Honda & Ishii, 1966).

Vascular labyrinths associated with the carotid arteries have been described in both fishes ('Siluriformes'; Srivastava & Singh, 1980; Olson, Flint & Budde, 1981) and lizards (van Bemelen, 1886; Beddard, 1905; Palme, 1934, 1935; Adams, 1953). There is no evidence, however, that the labyrinths in fish are associated with any form of receptor mechanism, and the description of the origin of the internal from the common carotid in lizards as a 'labyrinth', similar to that in anuran amphibians, is extending homology beyond actuality. In the majority of lizards, the internal carotid arises from the carotid arch by a variable number of openings forming communicating channels (Adams, 1958; Rogers, 1967). Between the main and collateral subdivisions of the common and internal carotid the adventitial connective tissue is thickened into a wedge-shaped mass. Although not a labyrinth, this tissue is highly vascular and is characterized by the presence of scattered groups of glomus and sustentacular cells (Adams, 1952; Rogers, 1967; Kobayashi, 1971*a*). This region is profusely innervated by the vagus, mostly from the superior laryngeal branch (Rogers, 1967), and perhaps also from the glossopharyngeal and cervical sympathetic nerves (Terni, 1931; Adams, 1958). Lizards increase breathing when presented with hypoxic and/or hypercapnic gas mixtures and blood of low O₂ tension injected into the junction of the carotid arch, via the external carotid artery, causes hyperventilation which is abolished by denervation of this region (Courtice, 1980).

In chelonians, as in birds, chemoreceptive tissue is not present at the extant carotid bifurcation. This is not surprising for the division is secondary. During embryological development in birds, the aortic arches retreat backwards and the carotid bifurcation remains close to the heart. However, the external carotids then atrophy and the internal carotids (generally called the common carotids) divide, secondarily, in the head region (West, Langille & Jones, 1981). Hence, in birds, the largest aggregations of chemoreceptive tissue, the carotid bodies, are found in the central cardiovascular area close to the parathyroid and thyroid glands (Abdel-Magied & King, 1978). The avian carotid body is innervated by one or more vagal branches from the nodose ganglion. Chemoreceptive tissue is active, even at normal arterial oxygen tensions, and in both birds and anuran amphibians, nerve discharge is random (Ishii *et al.* 1966; Bamford & Jones, 1976; Ishii & Ishii, 1976). Deafferentation of the carotid bodies reduces resting ventilation and prevents, or at least blunts, increases and decreases in breathing during short term exposure to environmental hypoxia and hyperoxia respectively (Jones & Purves, 1970*b*; Bouverot, 1978; Bouverot & Sébert, 1979; Lillo & Jones, 1982*b*). When there are no accompanying changes in breathing, such as during experimental diving in ducks, then carotid body chemoreceptor activation is expressed on the cardiovascular system. In domestic ducks, nearly all of the bradycardia and at least half of the increase in total peripheral resistance which accompanies forced submergence are prevented by carotid body deafferentation (Jones & Purves, 1970*a*; Jones, Milsom & Gabbott, 1982*a*).

The function of the other 'nests' of chemoreceptive tissue, spread throughout the central cardiovascular area, is unknown. In turtles and lizards there is chemoreceptor type tissue located in the truncal region, just upstream of the heart, supplied with blood

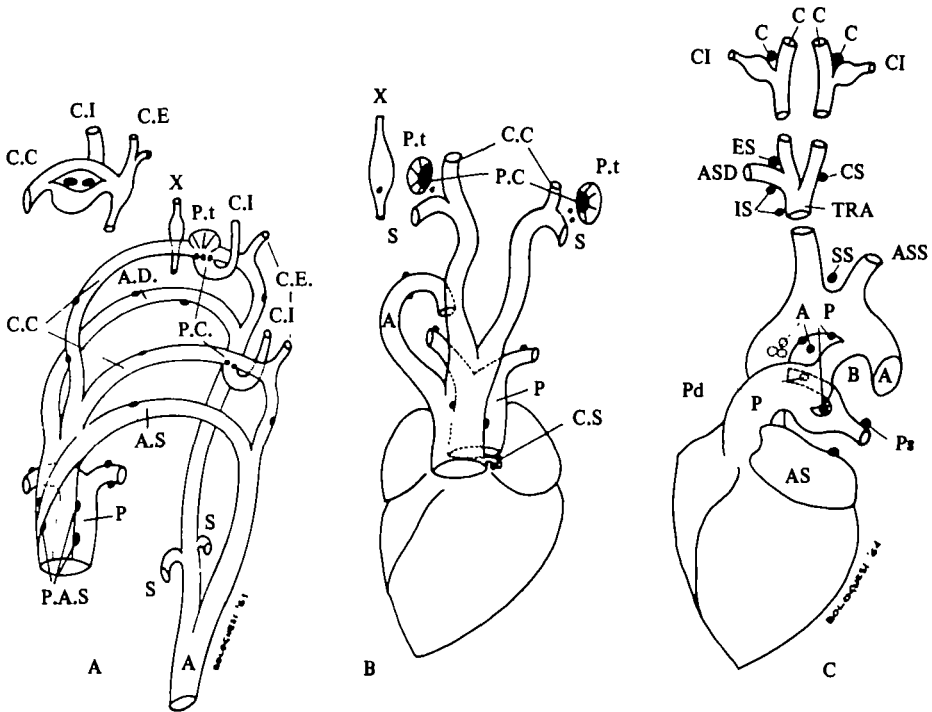


Fig. 6. Diagrams which show the distribution of some of the cervico-thoracic 'paraganglia' in Amniotes. (A) Saurian. Paraganglionic cells groups in black. P.A.S. = aortico-pulmonary paraganglionic cells groups. P.C. = paraganglionic cells groups homologous to the carotid paraganglion. P = Pulmonary artery. A.D and A.S = right and left aortae. C.C. = common carotid. P.t = parathyroid (represented only on the right side). C.I and C.E = internal and external carotids. S = subclavian artery. X = ganglion nodosum nervi vagi. A = descending aorta. Upper scheme, left: the dorsal wall of the bifurcation of the common carotid is opened; the internal carotid originates by means of two openings from the concavity of the common carotid. (B) Birds. C.S = coronary artery. Other abbreviations as in A. (C) Mammals. C = external carotid, CI = internal carotid. C = carotid body. ES, IS = right subclavian bodies. ASD and ASS = right and left subclavian arteries. CS = microparaganglion at the root of the left common carotid. SS = left subclavian paraganglion. AP = aortico-pulmonary paraganglia. Pd, Pa = right and left pulmonary branches. AS = left atrium. Other abbreviations as in A (from G. Muratori, 1962).

from the left aorta, and probably innervated by the superior laryngeal and vagus nerves (Adams, 1962; Fedele, 1935). Although this may function as a chemoreceptor, on the basis of physiological evidence Benchetrit, Armand & Dejours (1977) claim that the pulmonary artery is the most likely site of oxygen-sensitive chemoreceptors in the tortoise (*Testudo horsfieldi*). Stimulation of breathing or enhanced diving bradycardia, resulting from injecting cyanide into the pulmocutaneous arches of bullfrogs (*Rana catesbeiana*) also suggests that this arch supplies a chemoreceptive area (Lillo, 1980). Unfortunately, none of these results absolutely precludes other central locations (Chiba & Yamauchi, 1973). In reptiles (Chiba & Yamauchi, 1973; Yamauchi, Fujimaki & Yokota, 1975), and some birds (Tcheng & Fu, 1962; Tcheng, Fu & Chen, 1963a), 'glomus-type' cells have also been found within the aortic walls and even associated with cardiac ganglia. In turtles, some of these cells are in reciprocal synaptic

contact with postganglionic neurones of the cardiac ganglia (Yamauchi, 1977) and may play a role in modulating autonomic outflow to the heart (Yamauchi, 1979) rather than acting as part of a local chemosensory reflex. In birds there may be a large number of glomus cell nests in the aortic region alone (Fig. 6; Tcheng *et al.* 1963*a*) and Palme (1934) suggested that their total mass exceeded that of the carotid bodies. Some of these glomus cell groups have been likened to the aortic bodies of mammals since, unlike in reptiles, they are generally located outside of the blood vessel walls. The majority, if not all, of these cell groups receive blood from the aortic arch or coronary artery (Tcheng, Fu & Chen, 1963*b*). The function of these cell groups in respiratory and circulatory control is unknown.

Glomus type cells have been described in the pseudobranch of the selachian, *Torpedo mamorata* (Laurent, 1976) although elasmobranchs don't show a very marked ventilatory increase during hypoxia (Piiper, Baumgarten & Meyer, 1970; Butler, Taylor & Short, 1977). In teleost fishes, glomus-type cells have never been found in the central cardiovascular area (de Kock, 1963) yet these fish do show powerful ventilatory responses to environmental hypoxia or to cyanide injected into the ventral aorta (Eclancher, 1975; Eclancher & Dejours, 1975). Electrophysiological and histological evidence implicates the pseudobranch in teleost ventilatory responses (Laurent, 1967, 1969; Baretts, Dunel & Laurent, 1970; Laurent & Rouzeau, 1969, 1972), but destruction or deafferentation of the pseudobranch has no effect on the breathing responses accompanying environmental hypoxia, hyperoxia or hypercapnia (Hughes & Shelton, 1962; Randall & Jones, 1973; Bamford, 1974). In fact, with respect to the response to low levels of environmental hypercapnia, it is now felt that the ventilatory responses are related to CO₂-induced impairment of blood oxygen transport capability and are therefore elicited by an oxygen-sensitive receptor system (Dejours, 1972; Randall & Jones, 1973; Truchot, Toulmond & Dejours, 1980; Smith & Jones, 1982).

This oxygen receptor system, in both aquatic and air breathing teleosts, may be extremely diffuse (Johansen, 1970; Lahiri, Szidon & Fishman, 1970; Saunders & Sutterlin, 1971; Laurent, Dunel-Erb & Bailly, 1981). Certainly, a diffuse receptor system, innervated by cranial nerves V, VII, IX and X, causes bradycardia in response to environmental hypoxia in elasmobranchs (Butler *et al.* 1977). In teleosts, receptors restricted to the first gill arch, and innervated by cranial nerves IX and X, also cause bradycardia during hypoxia but do not affect breathing (Smith & Jones, 1978; Daxboeck & Holeton, 1978).

Johansen (1970) suggested that chemoreceptive sites should be different in aquatic as compared with air breathers because of the routinely unstable nature of the aquatic environment. Water breathers, in order to make appropriate adjustments, must be able to distinguish between changes initiated internally or externally. Yet, although teleosts respond to intravascular cyanide with hyperventilation and bradycardia, no response is shown when cyanide is placed in the inhaled water (Eclancher & Dejours, 1975), indicating the lack of an externally located oxygen sensor which affects breathing. Anuran tadpoles also hyperventilate during hypoxia, yet at a stage when the carotid labyrinth (the adult chemoreceptive site) has not yet developed (West & Burggren, 1982). Consequently, in aquatic breathers, the oxygen-sensitive chemoreceptive region may be a part of the central nervous system (Saunders & Sutterlin,

1971; Bamford, 1974) perhaps akin to the CO₂-sensitive regions in the brains of reptiles (Hitzig & Jackson, 1978) and birds (Sébert, 1979; Milsom *et al.* 1981).

(2) *Intravascular mechanoreceptors*

All regions of the central cardiovascular area have the potential for transmitting information about the mechanical status of the cardiovascular elements to the central nervous system by way of autonomic nerves. This potential is phylogenetically ancient, but, as the number of visceral arches which survive embryonic development is reduced from fishes to mammals, the mechanoreceptive sites are likewise restricted (Koch, 1931; Boyd, 1936).

In all vertebrates, the heart has a rich innervation and much of it appears to be sensory (Ábrahám, 1969). In mammals, the sensory receptor system consists of highly differentiated end structures in the form of terminal arborizations (compact or diffuse unencapsulated endings), end nets, and even encapsulated receptors. However, despite extensive investigation no sensory receptor nerve terminals of the mammalian type have been described in lower vertebrates (Ábrahám, 1969). In amphibian hearts, the nerve fibres which probably have a sensory function have been described as ending in rings, knobs or plates (Ábrahám, 1969; Kumar, 1971, 1974; Chourasia, 1972). Similar terminations have been seen in the avian ventricle (Mather & Mather, 1974) and Bogusch (1974*a, b*) described smooth nerve fibres, spirally wound around Purkinje fibres, which could be mechanoreceptors in the avian atrium. Thus, the sudden appearance of more complex receptor structures in mammals, with no obvious phylogenetic precursors, remains a puzzling step in the evolutionary biology of cardiac receptors (Ábrahám, 1969).

The cardiac receptors in anuran amphibians have been identified, by their excitation pattern and anatomical location, in all the cardiac chambers (Kolatat, Kramer & Mühl, 1957; Downing & Torrance, 1961). Atrial receptors are silent at low atrial pressures but both the frequency and period of receptor discharge increase with increasing pressure during systole (Neil & Zotterman, 1950; Kolatat *et al.* 1957; Downing & Torrance, 1961). Ventricular receptors, located at the base of the ventricle, discharge during the isometric phase of contraction and may fire again in late systole or during the isometric relaxation phase (Kolatat *et al.* 1957; Downing & Torrance, 1961). The number of nerve impulses increases with increasing rate of change in isometric pressure generation. In birds, electrophysiological recordings of afferent vagal nerve activity originating from receptors in the heart have also been made (Jones, 1969; Estavillo & Burger, 1973*a, b*). At normal arterial blood pressure almost half these receptors discharge slowly and randomly, others discharge with each heart beat. The proportion of receptors with irregular discharge patterns decreases markedly as the arterial blood pressure is raised (Estavillo & Burger, 1973*a*). Somewhat imprecise attempts at localization show that the main receptor area for this activity is the ventricle, near the base of the aorta, in the region of the aortic valve (Jones, 1969; Estavillo & Burger, 1973*a*). Many of the 'irregularly' discharging receptors are extremely sensitive to arterial CO₂ tensions, discharge falling with increases in CO₂ (Estavillo & Burger, 1973*b*). Histological studies of lower vertebrate hearts have shown extensive nerve plexuses. From analogy with the nerve net of the vertebrate skin

(Winkleman, 1960), such plexuses may be capable of detecting many different sensory modalities including changes in the functional state of the cardiac chambers. The CO₂-sensitive discharge pattern found in avian cardiac receptors perhaps emphasizes the multi-modal nature of sensory perception by nerve plexuses.

The reflex effects of stimulation of these receptors, however, remains unclear. In elasmobranchs, pinching the ventricle causes a fall in heart rate. Extreme cardiac distension in both elasmobranchs and teleosts, caused by increases in venous return, often raises heart rate; however, this increase is due to stretch of the cells of the pacemaker region, which depolarize more rapidly when extended (see Jones & Randall, 1978). In ducks (*Anas platyrhynchos*), increases in atrial or left ventricular diastolic pressure activate receptors which reflexly cause bradycardia and hypotension (Jones, Milsom & West, 1980). Activation of epicardial receptors by injection of nicotine tartrate into the pericardial cavity also causes bradycardia and hypotension in ducks as it does in mammals (Blix, Wennergren & Folkow, 1976; Jones *et al.* 1980), presumably by stimulating left ventricular receptors. It has been suggested that activation of these receptors by rises in left ventricular diastolic pressure during forced diving could cause an enhancement of diving bradycardia (Blix *et al.* 1976). Anaesthetization of these receptors by intrapericardial injection of local anaesthetic, in a concentration sufficient to block the response to nicotine but not the efferent vagal nervous pathway, however, has no effect on diving bradycardia (Jones *et al.* 1980). Furthermore, prevention of the rise in left ventricular diastolic pressure which normally occurs during forced diving, by withdrawal of blood from the great veins, also has no effect on either the initiation or maintenance of the bradycardia (Jones *et al.* 1980). In summary, cardiac receptors associated with extensive nerve plexuses are common throughout the lower vertebrates yet virtually nothing is known of their physiological function.

All terrestrial vertebrates, and many aquatic ones, show a barostatic reflex. If blood pressure is disturbed, it is restored to the former level by reflex effects on either cardiac output, peripheral resistance or both (Fig. 7). The occurrence of a barostatic reflex in aquatic animals, as well as in small terrestrial ones, shows it is an expression of a general circulatory compensatory mechanism and could not have evolved solely in response to the effects of gravitational stresses on the circulatory system. The ability to regulate blood pressure varies in accordance with the properties of the various control systems found in lower vertebrates. Thus in toads (*Bufo arenarum*), the output of the control system varies in proportion to the change in blood pressure (a proportional controller), whereas in lizards (*Tupinambis rufescens*) the output of the system also varies with the rate at which the pressure changes (Segura & Kacelnik, 1977). This rate response is a derivative component and is believed to reduce excessive 'hunting' in the control system. The efficacy of the barostatic control system is compromised by anaesthesia (Smith, Berger & Evans, 1981*a*) and also depends on what other demands are concurrently being made on the cardiovascular system (e.g. heat stress enhances regulation in the terrestrial snake, *Notechis scutatus*, Lillywhite & Seymour, 1978).

In light microscopy, baroreceptive nerve terminals appear as rings, knobs, fine filaments or flat expansions. Baroreceptors in the amphibian carotid labyrinth and those in the aortic and pulmonary arteries in snakes appear to be less complex than

those of birds and mammals (Boyd, 1942; Rogers, 1964; Ábrahám, 1969; Jones, 1973). In birds the characteristic dense end plates are circular, elliptic or triangular in shape (Jones, 1973) and are located in the *tunica adventitia* and the outer layers of the *tunica media* at the root of the aorta. The nerves giving rise to these endings in birds often enter the blood vessel wall accompanied by thin, smooth, sympathetic fibres (Ábrahám, 1969; King & King, 1978). Ultrastructurally, baroreceptor endings are axonal enlargements ($6.5\text{--}2.0\ \mu\text{m}$ in diameter) which contain few vesicles but many small mitochondria (King & King, 1978). The endings are partly invested by a Schwann cell which may be shared with an accompanying adrenergic fibre. These axonal complexes are associated with collagen and elastic fibres but not smooth muscle cells. Baroreceptor-type nerve endings have also been located in other regions of the arterial trunk and in the pulmonary artery in birds with the light microscope (Tcheng, Fu & Chen, 1965; Ábrahám, 1969), while with the electron microscope, encapsulated receptors which could be rapidly adapting, phasic baroreceptors have been identified in the wall of the common carotid artery of *Gallus* (Abdel-Magied, 1978*b*). Similar encapsulated structures may also have been seen with the light microscope in the amphibian carotid arch (Palme, 1934; Rogers, 1964).

Although the carotid arch of terrestrial vertebrates is homologous with the third branchial arch in fishes, in elasmobranchs, all arches have similar receptor properties (Irving, Solandt & Solandt, 1935). In teleosts, the first two branchial arches (homologous with the carotid and aortic arches in higher vertebrates) seem to be much more sensitive in terms of the cardiac inhibition caused by a given pressure increase than the last two arches (Ristori & Dessault, 1970). Surprisingly, these are the only examples of the carotid equalling the aortic baroreceptor control system until the evolution of the carotid sinus in mammals [given the qualification that little is known about the baroreceptive properties of the gills in urodeles (Lutz & Wyman, 1932*b*)]. In all other lower vertebrates, the carotid baroreceptors, if present, are of lesser importance.

In dogfish, baroreceptors are claimed to lie on the afferent side of the branchial arches (*Squalus acanthias*, Lutz & Wyman, 1932*a*) although efferent branchial arterioles, at their junction with the efferent arteries, have the richest nerve supply from the branchial nerves (*Mustelus canis*, Boyd, 1936). In teleosts, the ventral aorta does not appear to be an important reflexogenic zone (Ristori, 1970) while baroreceptor-type nerve endings have been found in all branchial arches, even in the efferent branchial vessels supplying the pseudobranch (Laurent, 1976). The afferent pathway for these receptors is the IX nerve for the first gill arch and the X for the other branchial arches. Baroreceptors are excited both by the absolute pressure level and the rate of change in pressure, discharging in systole at pressures at which they are silent in diastole. In elasmobranchs, however, baroreceptor discharge quickly ceases if a steady pressure is maintained in the branchial arch (Irving *et al.* 1935) and the rapid adaptation characteristics of these receptors probably explains why raising pressure in the branchial arches only causes a transient cardiac inhibition (Lutz & Wyman, 1932*a*). Only transient baroreceptor-induced cardio-inhibition occurs in teleosts (Mott, 1951), implying rapid baroreceptor adaptation as well, but, unlike elasmobranchs, some teleosts appear to be able to tolerate long term gravitational stresses (30 min head-up tilt-in-air, gills artificially perfused; Ogilvy & DuBois, 1982). The efferent pathway for

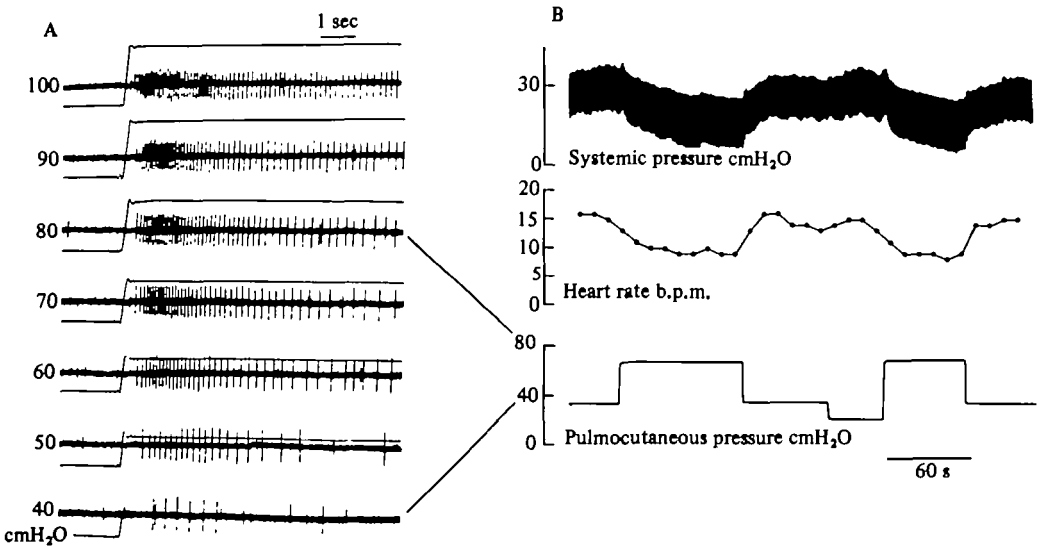


Fig. 7. (A) The response of pulmocutaneous arch baroreceptors, in an anuran amphibian, to distension of the vascularly isolated arch at a range of static pressures (from Ishii & Ishii, 1978). (B) The nerve discharge in A is correlated with the effects on blood pressure and heart rate of distending the vascularly isolated pulmocutaneous arch (N. H. West & B. Van Vliet, unpublished observations).

cardio-inhibition is the cardiac branch of the vagus and the reflex is both hetero- and homolateral in elasmobranchs (Lutz & Wyman, 1932*a*), whereas in the carp (*Cyprinus carpio*), the reflex is predominantly heterolateral (Ristori, 1970). Attempts to show the innervation and mimic the action of baroreceptors by electrical stimulation of the cut central ends of the branchial nerves have been compromised by the presence of other mechanoreceptors and chemoreceptors in the gills and surrounding branchial areas (Smith & Jones, 1978) which also cause cardiac inhibition on stimulation.

Low sensitivity receptors in the carotid labyrinth of anuran amphibians (Neil *et al.* 1950; Ishii *et al.* 1966) also cease discharging when exposed to a steady pressure. These baroreceptors are low sensitivity in that their threshold for excitation exceeds the normal systolic pressure (Ishii *et al.* 1966) and, when stimulated artificially, have no apparent short term circulatory effects in either anaesthetized or unanaesthetized toads (*B. vulgaris*, Ishii *et al.* 1966; *B. arenarum*, Segura, 1979; *B. marinus*, Smith *et al.* 1981*a*). In anurans, receptors participating in the barostatic reflex are located in the pulmocutaneous artery and are innervated by a branch from the laryngeal nerve (Fig. 7; Neil *et al.* 1950; Ishii & Ishii, 1978; Smith *et al.* 1981*a*; West & Van Vliet, unpublished). These receptors have a threshold of excitation of about 30 mmHg (Ishii & Ishii, 1978). This is lower than the normal diastolic pressure so the receptors are always active. The maximum sensitivity of these receptors appears to be in the range of 40–50 mmHg, the normal blood pressure range in *Bufo vulgaris* (Ishii & Ishii, 1978), with rates of adaptation varying from fibre to fibre. Sectioning the laryngeal nerve causes an increase in systemic arterial pressure in anaesthetized toads (Ishii & Ishii, 1978) and, in unanaesthetized animals, blood pressure is extremely variable after

denervation or vascular isolation of the pulmocutaneous arches (West & Van Bliet, unpublished observations).

Only two studies have recorded from baroreceptors in reptiles (Kamenskaya, Samonina & Udel'nov, 1977; Faraci *et al.* 1982), both confirming earlier morphological and physiological observations that baroreceptors are located close to the heart, in either the truncal region (Fedele, 1935; Adams, 1958) or the base of the pulmonary artery (Faraci *et al.* 1982). In chelonians, the truncus is innervated by superior and inferior truncal nerves which arise from the superior laryngeal nerve and nodose (or truncal) ganglion of the vagus respectively. These nerves form adventitial and medial terminal plexuses with a variety of endings and do not continue to the heart (Fedele, 1935; Adams, 1962). Both truncal nerves have a depressor function. By inflating cuffs around the major arteries, Berger, Evans & Smith, (1980), were able to confirm the presence of baroreceptive zones in either the truncus or cardiac chambers in the lizard, *Trachydosaurus rugosus*. Haemorrhage and tilting have also been used in both snakes (Fig. 8) and lizards to investigate the properties of the barostatic control system (Hohnke, 1975; Seymour & Lillywhite, 1976; Lillywhite & Seymour, 1978; Lillywhite & Smith, 1981). All these investigations suggest that the sympathetic nervous system predominates in both cardiac and peripheral vascular control in reptiles. An interesting conclusion from 'tilt' experiments with snakes is that aquatic snakes, besides having lower blood pressure than non-aquatic species, also have poorer barostatic regulation or no regulation at all (Seymour & Lillywhite, 1976). These experiments however may be deceptive. If the baroreceptors are located just outside the heart in snakes, as in other reptiles, then the amount by which baroreceptors will be affected during a tilt will depend on the position of the heart with respect to the mid-point of the body (the point of hydrostatic neutrality). In non-aquatic snakes the heart is close to the head while in aquatic species it lies in the mid-body position (Fig. 8). Hence, in aquatic snakes, the baroreceptors will 'see' no intravascular pressure changes in response to tilting and therefore reflex changes in blood pressure should not be expected (Fig. 8). On the other hand, Boyd (1942) has suggested that the carotid bifurcation, in addition to the aorta and pulmonary artery, is a baroreceptive region in the snake, *Vipera berus*, which, if true of all ophidians, confounds the above argument.

In ducks, even several weeks after bilateral section of the 'aortic' (or depressor) nerves, there is only a 20% increase in mean arterial pressure although resting heart rates may double (Jones, 1973; Lillo & Jones, 1982*a*). Bilateral depressor nerve section also prevents reflex bradycardia in response to induced systemic hypertension (Jones, 1973) which confirms the view of Durfee (1964) and McGinnis & Ringer (1966) that the carotid body area in birds cannot be a pressor reflexogenic zone. It has been suggested that the profound diving bradycardia found in ducks is due to a barostatic reflex operating in response to a chemoreceptor-induced increase in peripheral resistance (Andersen & Blix, 1974). Studies on both acute (Jones *et al.* 1982*b*) and chronic barodenervates (Jones, 1973; Lillo & Jones, 1982*a*), however, show that an intact barostatic reflex is not crucial for development of the substantial portion of the cardiovascular response to forced submergence in ducks.

A number of studies have attempted to compare the efficacy of the barostatic control system in vertebrates. These attempts are beset with a number of problems not the

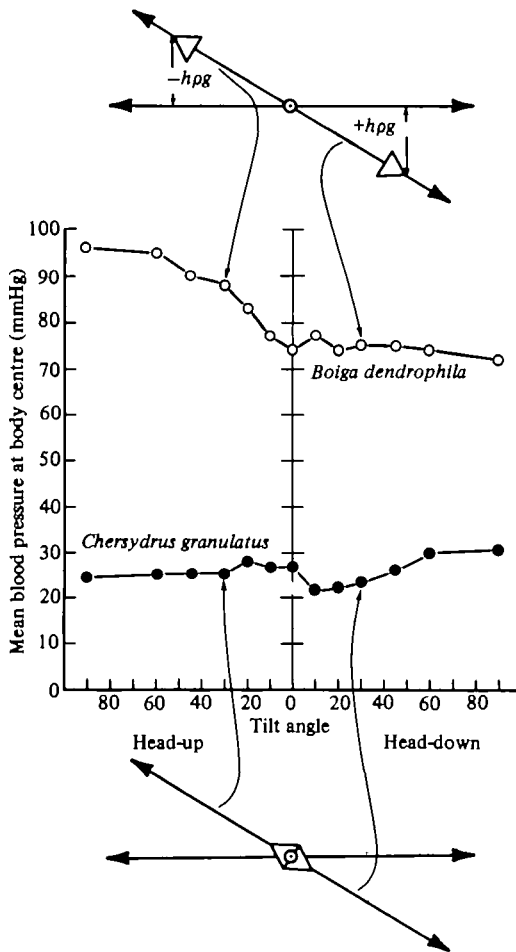


Fig. 8. Mean arterial blood pressure at the body centre in two snakes as a function of tilt angle. The arboreal snake (*B. dendrophila*) apparently shows much better regulatory capability than the aquatic snake (*C. granulatus*). However, truncal baroreceptors in the arboreal snake are subjected to a much greater pressure change ($\pm hpg$, insert over) than those in the aquatic snake (insert below) because the heart (symbolised by Δ) is much closer to the head (symbolised by \uparrow). (Data from Seymour & Lillywhite, 1976).

least of which seems to be the lack of the realization that baroreceptors control blood pressure and not heart rate, stroke volume or peripheral resistance. The last three are only components of the total effector arm of the barostatic reflex. Millard & Moalli (1980) found that the heart rate response to blood pressure changes in the turtle (*Pseudemys scripta elegans*) was more than twice that found in the bullfrog (*R. catesbeiana*). Besides only analysing one component of the cardiovascular response, these authors also, unfortunately, measured systemic arterial pressure in the bullfrog while the receptors are located in the pulmocutaneous arch. Although the frog heart is undivided, seldom are mean pressures or the rate of change in pressure in both arches the same (Shelton & Jones, 1965). A similar problem exists with the study of Smith

et al. (1981 *a*) with the toad (*B. marinus*). On a more positive note, however, Smith *et al.* (1981 *a*) have shown that using 'normalized' gain allows more meaningful comparisons between species with widely different heart rates. 'Normalized' gain expresses the relation between heart rate and blood pressure in terms of the percentage change in heart rate per unit change in mean arterial pressure. Bearing in mind the restricted value of measurements of only one component of the effector response, 'normalized' gain for toads is about 1%/mmHg (Smith *et al.* 1981 *a*) which compares with 7.2%/mmHg in the lizard and 2-5%/mmHg in dog, rabbit and man (Berger *et al.* 1980). It must also be kept in mind that the expression of the various parts of the effector arm of the barostatic reflex may be compromised by the experimental technique, e.g. use of vasoactive drugs, which prevent normal adjustments in the peripheral vasculature. Furthermore, changes in conditions during an experiment may also affect input: output relationships. For instance, stimulating the central end of a cut depressor nerve in ducks gives a similar proportionate fall in heart rate before, during and after diving, yet the proportionate reduction in mean arterial pressure after 2 min submergence is only half what it is before the dive (Jones *et al.* 1982 *b*). Therefore, it must be concluded that, at present, the relevance of comparative observations to understanding the development of the barostatic control system, from a phylogenetic perspective, remains obscure.

CONCLUDING REMARKS

So many gaps remain in our knowledge of the role of peripheral receptors in cardiovascular and respiratory control that virtually every investigation, if adequately designed, makes an important contribution to our understanding of the phylogenetic background in both physiology and morphology. Also, many less obvious and more subtle controls remain to be elucidated. For instance, muscle or joint receptors may make an important contribution to elevations in cardiovascular or respiratory performance during exercise, an excitatory reflex not broached in the present discussion. Furthermore, we have only hinted at the possibility of interaction between the various reflexes we have discussed in isolation. Chemoreceptor: baroreceptor interactions have been the subject of investigation in fish (Wood & Shelton, 1980) and in diving ducks (Jones *et al.* 1982 *b*) and an obvious future direction in research is to bring an integrative approach to more studies of control in lower vertebrates (Korner, 1971).

The role of peripheral receptors in short-term regulation seems obvious. What is considerably more perplexing is the role these receptors play in cardiovascular and respiratory regulation over prolonged time periods. Ducks deprived of baroreceptors for several weeks do not develop severely elevated blood pressures (Lillo & Jones, 1982 *a*). Ducks also show increases in breathing in hypoxic conditions even after carotid body denervation (Jones & Lillo, in preparation). Furthermore, even the vitally important and extremely complex series of reflexes which participate in the diving response can be overruled by conditioning (G. R. J. Gabbott & D. R. Jones, in preparation) and considerably altered in expression in the wild (Butler & Woakes, 1979). Thus peripheral receptors could be viewed merely as the 'fine-tuners' of cardiovascular and respiratory patterns which are initiated and maintained by hormonal or humoral changes both within and without the central nervous system. Whether this supposition has any basis must be left to the future.

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