The control of breathing in birds with particular reference to the initiation and maintenance of diving apnea[1,2]

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The central and peripheral control of breathing in birds has recently been the subject of intensive investigation. Reviews by Fedde and co-workers (35), Jukes (55), and Lasiewski (58), complemented by the report of the workshop in Göttingen on *Receptors and control of respiration in birds* (41), give a comprehensive evaluation of the present state of knowledge. In view of these published reports it seems superfluous to tramp once more over such well-trodden ground, and so the emphasis of this review has been moved from control of breathing movements to cessation of breathing. Apnea is most commonly observed in birds during performance of feeding maneuvers, particularly if these involve submergence of the head. Under experimental conditions, apnea may be induced by a large number of factors in both diving and nondiving species, and many of the mechanisms that may contribute to diving apnea are also present in nondivers.

The apneic periods that birds can endure range from less than 1–3 min in the chicken and pigeon (14, 15) to 12–15 min for the guillemot (14) and domestic duck (3, 69). In diving birds apnea is maintained in the face of values for blood oxygen, carbon dioxide, and pHa that would stimulate breathing if the animals were subjected to these same levels while allowed access to air (20–22, 53, 54). In fact, Butler and Taylor (22) concluded that the duck is more sensitive to hypercapnic hypoxia in terms of the increase in minute volume breathed than is the chicken.

Aside from contributions of higher nervous centers to apneic responses that may occur in naturally diving animals there is no doubt that many peripheral reflex mechanisms can evoke an apneic response. Obviously integration of these peripheral mechanisms occurs in the brain and electrical stimulation of discrete suprabulbar or medullary areas can activate either afferent, efferent, or integrative centers. Feigl and Folkow (36) describe inducing apnea by electrical stimulation of an area in the mesencephalon in anesthetized ducks. A closely similar response is provoked by stimulation of a ventral hypothalamic area (37). Stimulation of a thalamic area ventromedial to the *nucleus rotundus* initiates immersion of the head and neck in the awake duck in water and feeding behavior patterns on land (37). This contrasts with stimulation of the ventral part of the hypothalamus in the awake duck, which causes "huddling up." Folkow and Rubenstein (37) speculate that since diving-like respiratory and cardiovascular adjustments can be induced by suprabulbar stimulation the possibility of an anticipatory activation of the bulbar diving reflex is indicated. Kotilainen and Putkonen (56) evoked respiratory depression in chickens by stimulating several suprabulbar sites. Stimulation of the mesencephalic quintofrontal tract caused apnea, and therefore participation of a trigeminal reflex mechanism in respiratory inhibition is strongly implicated (4). Cohen and Schnall (23) consistently obtained apnea by electrical stimulation of the solitary tract and a region of the commissural nucleus of Cajal in the pigeon medulla, which was not the case with stimulation of the lateral dorsal motor nucleus. Since stimulating the central end of the cut vagus produces respiratory arrest these sites may lie in afferent relay areas although, as Cohen and Schnall (23) point out, the evidence is far from conclusive.

THE AVIAN RESPIRATORY PACEMAKER

As in mammals the primary respiratory neurons are located in the medulla and function adequately after removal of the cortex or cerebrum (73, 75). Richards (72) and Peek and Phillips (66) describe an area bilaterally situated in the anterior dorsal midbrain that promotes polypnea when stimulated even in vagotomized animals. The location of this site relative to other brain stem structures suggests a homology with the pneumotaxic center in the mammalian pons (71).

A detailed consideration of the avian respiratory pacemaker and its modulation by various afferent inputs is central to our theme. The respiratory pacemaker has been studied by Kuna et al. (57) using animals on unidirectional ventilation (Fig. 1). Using air flows 9–10 times

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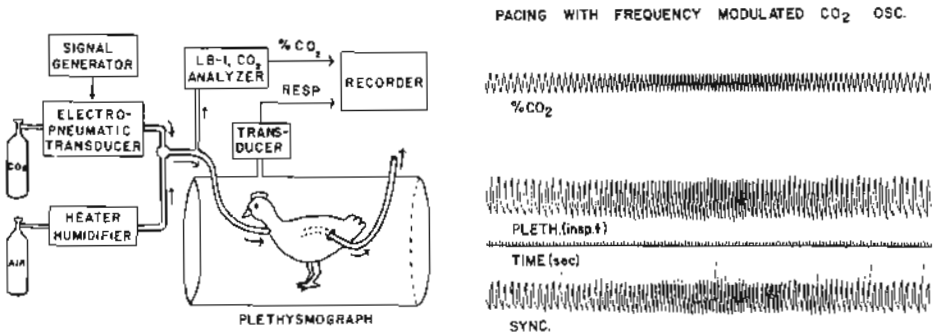
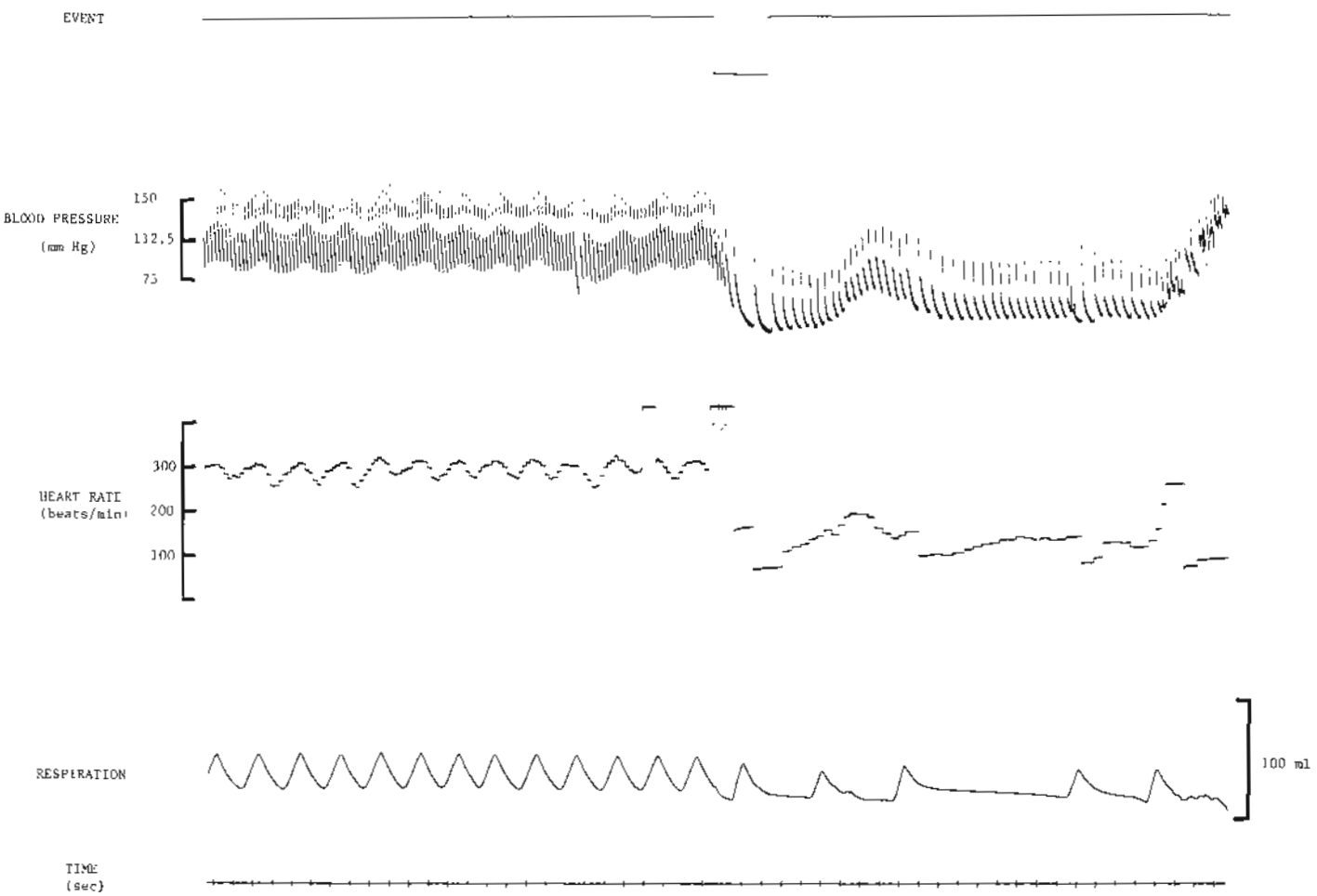


Figure 1. *Left*: unidirectionally ventilated chicken preparation used by Kunz et al. (57). *Right*: representative traces from an experiment showing pacing with frequency modulated CO_2 oscillations. Traces, from top to bottom: CO_2 oscillation; plethysomographic recording of respiratory movements; time, in seconds; and a measure of synchronization between the CO_2 oscillations and respiratory movements (57, by permission).

the normal minute volume, so that oxygen removal and CO_2 input by the chicken left the air crossing the gas exchanger effectively unchanged, they tested the effects on breathing movements of externally introduced pulses of CO_2. These pulses, either of constant amplitude at varying frequency or vice versa, could pace the normal respiratory movements indicating the system to be sensitive to CO_2 (Fig. 1). Furthermore, they showed that peaks of CO_2 level produced by the animal lock onto peaks of CO_2 produced externally, indicating that the system tends to maximize rather than minimize CO_2 oscillations. Kunz et al. (57) conclude that the avian respiratory pacemaker is an information loop acting like a ring oscillator, which runs from the brain to the respiratory muscles to a peripheral CO_2 receptor and back to the brain. Undoubtedly CO_2 sensitive receptors are present in avian lungs (32, 33, 67) but if CO_2 levels are held constant on unidirectional ventilation, maintaining normal levels of Pa_{CO_2}, birds continue to breath so there must be a backup oscillator that may be driven by O_2 receptors.

The physiological significance of the backup oscillator can be assessed by experiments in which the lungs are denervated while other vagally innervated reflexogenic zones, such as the arterial chemoreceptors, are left intact (Fig. 2). Lung denervation provokes bradycardia, hypotension,

Figure 2. The effect on arterial blood pressure, heart rate, and breathing of instantaneous lung denervation performed at the deflection on the event channel. Following unilateral cervical vagotomy the pulmonary branches of the vagus on the left side (six branches in this case) were dissected free from surrounding tissues and snared with cotton loops under general anesthesia. After closing the chest the animal was allowed to recover to a light plane of anesthesia and instantaneous denervation was effected by pulling on the six snares simultaneously (10).



and a tendency to apneustic breathing which resembles the breathing pattern observed following bilateral vagotomy (8, 74), indicating that backup systems are not particularly effective. After selective lung denervation normal respiratory rhythms can be induced by generalized body stimulation, and in the absence of this stimulation the animal may die. However, chronic denervates assume a more normal respiratory pattern 4 or 5 days after denervation (10).

That the respiratory neurons are sensitive to some form of pulmonary afferent feedback can be confirmed by monitoring the motor output of these neurons. In artificially ventilated, curarized ducks the motor output recorded in an intercostal nerve sometimes exhibits two periods, one being the intrinsic rhythm and the other matching the pump frequency, although more usually the intrinsic rhythm is reinforced by and locks onto the pump frequency. The respiratory neuron modulation produced by artificial ventilation is reduced by increasing CO_2 in the ventilating gas and disappears when inspired CO_2 levels reach about 7% (Jones and Bamford, unpublished). No modulation of respiratory neuron output during artificial ventilation can be provoked in bilaterally cervical vagotomized birds.

The motor output of the central respiratory neurons has also been studied by recording from both expiratory and inspiratory muscles and their innervation (35). Low pulmonary CO_2 causes apnea and diminished electrical activity in nerve and muscle, whereas raising CO_2 to 5–14% causes phasic muscle contraction and selective recruitment of motor units with increased activity in both nerve and muscle. This seems entirely reasonable in that tidal volume would be expected to increase under these conditions.

In the normal animal the respiratory muscles bring about the CO_2 oscillations that, according to the model of Kunz et al. (57), are necessary for maintenance of rhythmic breathing, but proprioceptive feedback from these muscles may also be important in the control of breathing rate and force. These feedbacks may be eliminated by using unidirectionally ventilated, paralyzed birds and, under these conditions, the central respiratory periodicity to normoxic hypercapnia may differ markedly from that observed when normally breathing birds are exposed to these gas mixtures. In ducks increases in Pa_{CO_2} from levels of 35–40 mm Hg cause a reduction in the periodicity of the central respiratory neurons and in some individuals respiratory neuron discharge stops when steady state Pa_{CO_2} exceeds 60 mm Hg (51). Bilateral cervical vagotomy eliminates these rate changes in response to elevated Pa_{CO_2} and calls into question whether ducks possess a central chemosensory area in the medulla as has been shown to exist in mammals (63, 64).

The above response, engendered when there is considerable reduction in feedback from pulmonary afferents or respiratory muscle/thoracic cage afferents, is even more striking when the central respiratory neuron discharge is monitored in paralyzed animals that are made asphyxic. Under these conditions a great difference is observed between the responses of diving and nondiving species. In many chickens the rate or number of impulses per burst increase dramatically in asphyxia, whereas in the duck burst size appears unaffected and rate falls, the bursts stopping in many individuals after 60–90 sec asphyxia (Fig. 3). This is most surprising, for the levels of Pa_{O_2}, Pa_{CO_2} and pHa obtained after 90 sec asphyxia in ducks provoke a large increase in minute volume if the animal is normally breathing a gas mixture yielding these same blood gas

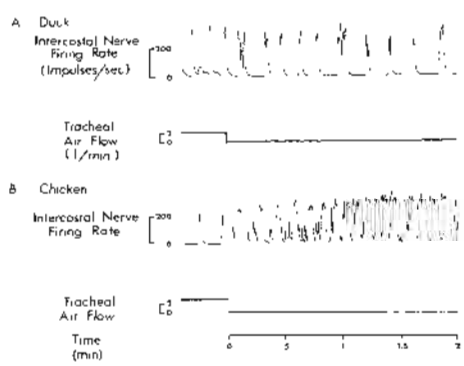


Figure 3. Respiratory motor activity, monitored from an intercostal nerve, during a 2 minute asphyxic period in a paralyzed duck (*A*) and paralyzed chicken (*B*). The asphyxic period commenced when the unidirectional ventilating air flow was stopped and is indicated by the deflection of the tracheal air flow trace (51).

tensions (21, 22). The inhibition occurring in this situation, which approximates that of a dive, may be the most important single factor in promoting apneic endurance in divers compared with nondivers.

PERIPHERAL INFLUENCES AFFECTING BREATHING

Widdicombe (76) made a detailed survey of a large number of stimuli, affecting receptors in the airways, lungs, or cardiovascular system of mammals, whose output caused pronounced reflex changes in breathing. Similar stimuli would affect these receptors in birds and it is therefore convenient to adopt Widdicombe's (76) scheme in assessing the role that these stimuli might play in initiation or maintenance of apnea.

Respiratory reflexes from the musculoskeletal system

In mammals the initial cardiovascular and respiratory responses to exercise result from a reflex arising in the exercising limbs (2, 25–27) although cortical influences may also make a contribution (40). The receptors involved are those within the muscles themselves and the joints (12, 25, 27). Birds frequently exhibit a close synchrony between wing muscle activity and breathing (13), although in some species this linkage may have a mechanical component as is exemplified in the 1:1 relationship between wing beat and breathing frequencies in pigeons during flapping flight (ms in preparation, P. J. Butler, D. R. Jones and N. H. West). In nature diving birds are variously active when submerged. The underwater progression of penguins has been described as "flying in water" but apnea is maintained in spite of possible input from the musculoskeletal receptors. Obviously, factors that institute and maintain apnea in divers are sufficiently powerful to overrule this stimulatory reflex.

Respiratory reflexes from the lungs

Cohn, Krog and Shannon (24) suggested that cessation of thoracic motion is the initiating factor in the cardiopulmonary responses to submergence in geese but their records of increase in air sac pressure during

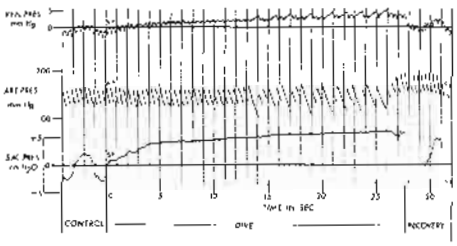


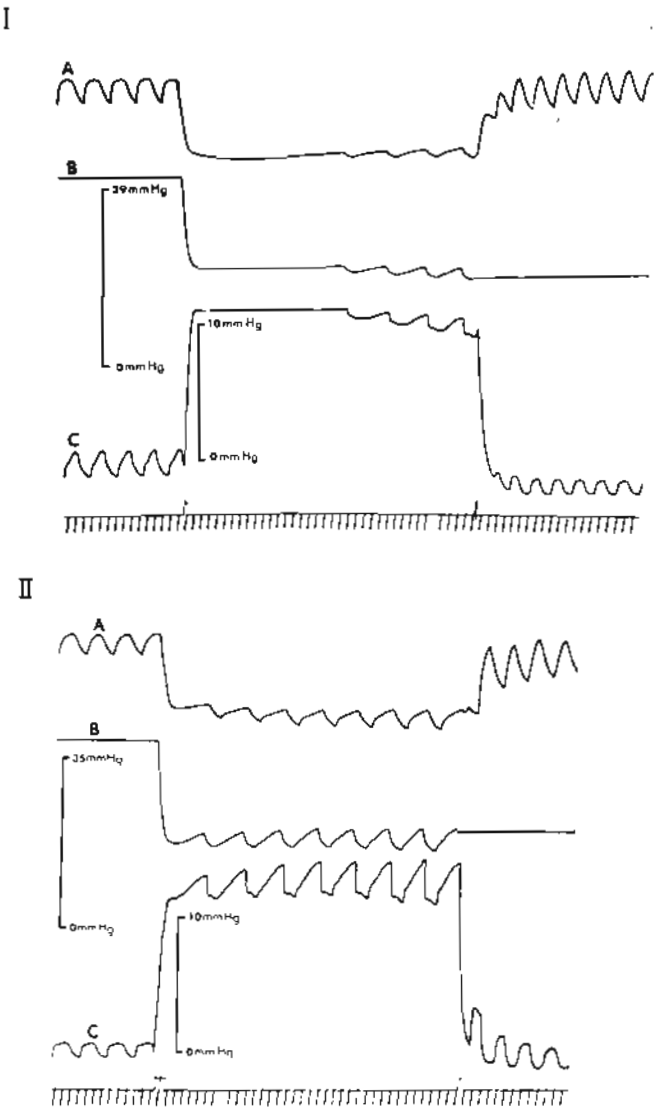
Figure 4. Traces illustrating the changes in venous and arterial blood pressures and pressure in the anterior air sac during a short dive in a goose. VEN PRES = central venous pressure, mm Hg; ART PRES = arterial pressure, mm Hg; SAC PRES = pressure in anterior air sac, cm H_2O. (24, by permission).

diving suggest that a contribution to the diving apnea may come from a Hering-Breuer type reflex (Fig. 4). The existence of a Hering-Breuer inflation reflex in birds is controversial. If the lungs are inflated with air then apnea ensues whereas if 7–8% CO_2 is added to the inflating gas then virtually no respiratory inhibition occurs (Fig. 5; 29). In mammals inflation with CO_2–air gas mixtures appears to have no effect on the Hering-Breuer inflation reflex (29), although Younes et al. (77) have shown that using these gas mixtures reduces duration of apnea in the cat due to increased inspiratory–excitatory influences. In birds inhibition of breathing also follows abrupt removal of CO_2 from a unidirectional artificial ventilating gas stream (68) but the inflation reflex differs from the so-called hyperventilation apnea (68) in that the former is abolished by bilateral cervical vagotomy (29) or selective lung denervation (10) whereas the response to the latter is an order of magnitude slower but still occurs, indicating the presence of CO_2 sensitive sites other than in the lungs or peripheral circulation.

Since the discharge of many intrapulmonary receptors, in spontaneously breathing birds, is inhibited by addition of CO_2 to the inspired air (17, 33) then an adequate explanation for the loss of the inflation reflex when CO_2 is added to the inflating gas can be provided in terms of this inhibition. However, inflation or deflation receptors insensitive to CO_2 have also been recognized (33, 59). An unresolved question is whether the animal is using these CO_2-sensitive receptors as "stretch receptors" or as "carbon dioxide sensors." It is certainly interesting to speculate that in some distant evolutionary stage lung receptors may have responded to both stretch and CO_2 but, since bird lungs are relatively inexpansible, CO_2 became the chosen modality to signal lung inflation sequences in birds while stretch was chosen in mammals. The cyclical discharge from pulmonary receptors in birds may be interpreted in terms of fluctuations in CO_2 throughout the breathing cycle, CO_2-sensitive receptors being stimulated when fresh air is breathed in and inhibited when CO_2 concentration in the lung rises towards the end of inspiration (33). Furthermore, even in mammals, pulmonary stretch receptor discharge is depressed somewhat by increased end-tidal P_{CO_2} (65) which can be cited in support of Burger's (17) suggestion that, in the lungs of chicken, the receptors regulating respiration are CO_2-modulated mechanoreceptors.

Regardless of the modality of the stimulus, inflation of the lung–air sac system is accompanied by a massive vagal afferent discharge from pulmonary receptors which causes an inhibition of breathing. But diving apnea is maintained whether a dive is started with the lungs inflated or totally deflated (intrapulmonary pressure = atmospheric). Furthermore, although CO_2 insensitive receptors have yet to be monitored in apnea the CO_2 sensitive type cease discharge with the onset of diving apnea and therefore do not appear to be candi-

Figure 5. Respiratory response of a white leghorn chicken to inflation of the respiratory system with air (*I*) and air + 6% CO_2 (*II*). *A*) Sternal movements; inspiration down, expiration up. *B*) Pressure in inflating carboy. Drop occurs when gas is released into respiratory system. *C*) Intra-abdominal pressure. Time line, in seconds. (29, by permission).



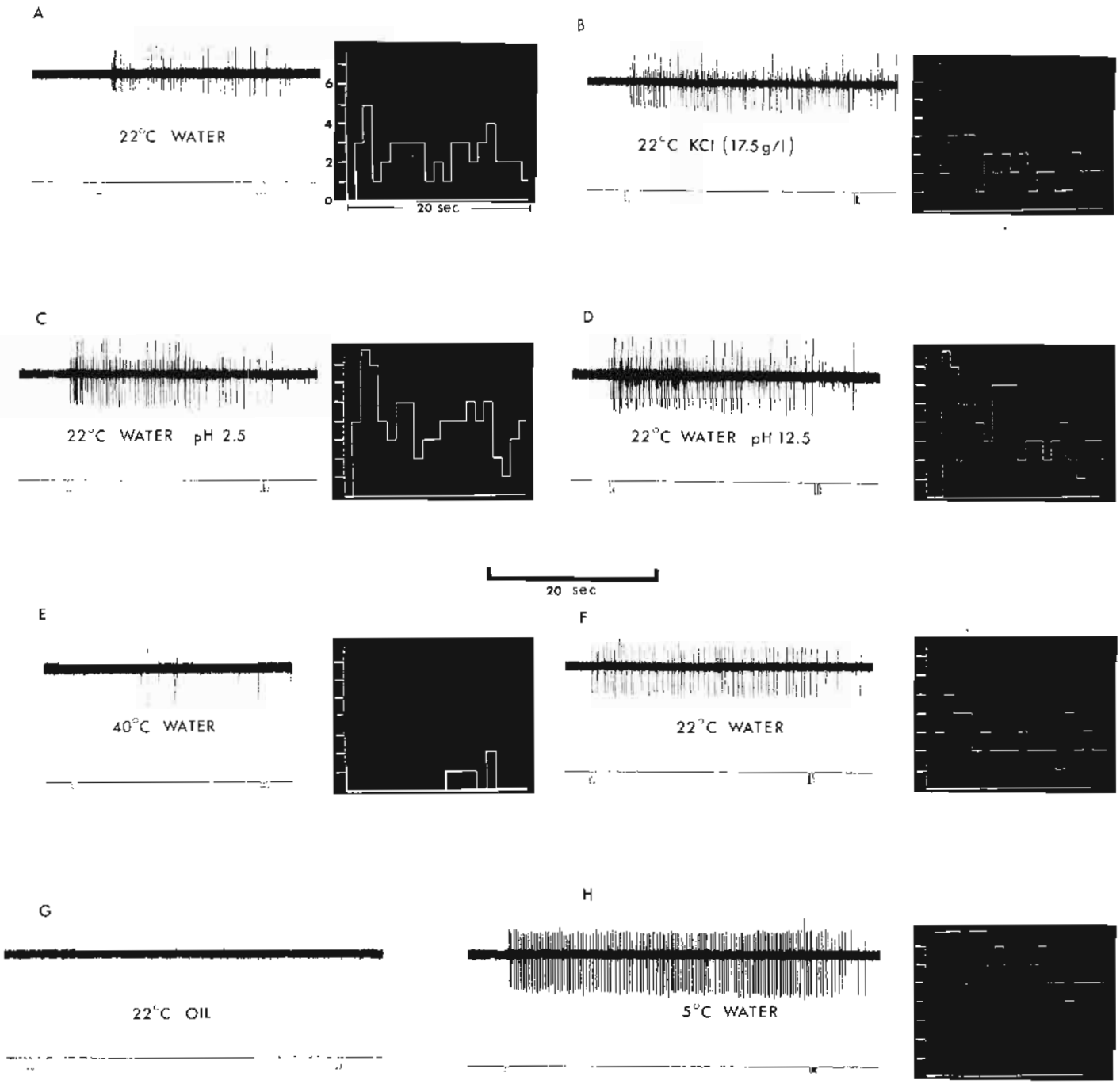


Figure 6. Traces illustrating the discharge characteristics of a nonadapting receptor in response to various aqueous solutions and paraffin oil being passed through the glottis at the same pressure. The upper trace is the electroneurogram and the lower an event marker (two marks = application of stimulus; three marks = stimulus withdrawn). Each trace is accompanied by a zero order, time-interval histogram (T.I.H.) of the two largest spikes present in the electroneurogram. The ordinate on the T.I.H. shows the number of discharges occurring in each 1 sec time bin, during the first 20 sec of stimulation. The time marker (20 sec) located in the middle of the figure indicates the time base of the electroneurograms (9).

dates for sending the appropriate afferent message for inhibition of breathing (11).

Reflexes from the upper respiratory tract

The application of noxious stimuli to the upper respiratory tract causes marked respiratory depression in both birds and mammals and the receptor sites in birds appear to be innervated by the trigeminal (4, 9), glossopharyngeal (9, 53), vagal (42), and hypoglossal nerves (62). Passage of dry, cold air through the trachea of a chicken in an expiratory direction slows breathing (29, 42), whereas if the air is first warmed and humidified no effect on breathing is observed (29). In the duck, water in contact with the internal respiratory passages invariably inhibits inspiration (20, 46, 47) with enhancement of expiratory intercostal muscle activity (62). Leitner et al. (62) attribute this response to thermoreceptors located in the skin of the bill (43, 60, 61) and innervated by the trigeminal nerve. However, the role of the trigeminal nerve in generation of diving apnea (4) is complemented by the activity of glottal afferents (9). Electrical stimula-

tion of the trigeminal nerve alone provokes only slight respiratory disturbance (70) compared with the apnea induced by bilateral electrical stimulation of the cranial cut ends of the glottal branches of the glossopharyngeal nerves (53). Initiation of diving apnea could be due to thermoreceptors or mechanoreceptors in the glottis (62) although the adaptation characteristics of these receptors would seem to preclude them from a major role in maintenance of diving apnea. However, Bamford and Jones (9) have isolated a unit from the glottal nerve, tentatively classified as a cold receptor, whose discharge characteristics (Fig. 6) closely paralleled the responses shown by the animal to application of oil, or warm, room-temperature, or cold water to the glottis. Prolonged apnea was rarely initiated with oil or warm water which also failed to elicit receptor discharge. Application of room-temperature or cold water to the glottis, however, initiated both strong receptor discharge (Fig. 6) and prolonged apnea. On the other hand, submerging intact ducks in warm water causes sustained apnea which indicates that cortical influences are probably important in the respiratory adjustment to diving (5, 9).

Respiratory reflexes from the cardiovascular system

Mechanoreceptor reflexes

The increase in venous pressure that occurs during a dive (Fig. 4; 24, 38, 48, 50) coupled with the increase in heart size (1) could stimulate venous or cardiac receptors (30, 31, 49). There is no doubt that the chicken ventricle is innervated by receptors basically similar in discharge pattern to those of mammals (30) although these receptors must be end-net receptors, since complex unencapsulated receptors do not exist in the chicken heart. In mammals the respiratory response provoked by the above stimuli would tend to be hyperpnea. In birds the respiratory influence of these receptors is unknown although a point of interest is that the activity of cardiac receptors studied by Estavillo and Burger (31) is depressed when Pa_{CO_2} is raised. The influence of arterial baroreceptors on breathing in birds is also unknown although denervation of aortic baroreceptors appears to have no influence on the ability of ducks to remain apneic during submergence of approximately 2 min duration (50). Consequently, it would appear that an increase in blood pressure that sometimes occurs at the start of a dive would not reinforce the apnea induced by glottal stimulation.

Arterial chemoreceptor reflexes

Arterial hypoxia and hypercapnia, alone or combined, provide a powerful stimulant to breathing in birds. It appears that the response of an-

TABLE 1. Changes in respiratory frequency and tidal volume in response to hypercapnia (upper table) and hypoxia (lower table)

	Control			Hypercapnia					
	No	Respiratory frequency, no./min	Tidal volume, ml	No.	Respiratory frequency, no./min	Tidal volume, ml	Change in respiratory frequency, %	Change in tidal volume, %	Notes
Duck	8	14.6	31.8	8	19.7	66.3	+35	+108	Normoxic hypercapnia Pa_{CO_2} = 43.1 mm Hg
Duck	5	11.25	49.0	4	8.33	137.5	−26	+180	Breathing 6–9% CO_2
Duck	10	20.1	19.6	10	13.0	60.1	−35	+206	Normoxic hypercapnia Pa_{CO_2} = 55 mm Hg
Chicken	8	19.3	22.9	8	21.0	56.0	+9	+144.5	Normoxic hypercapnia Pa_{CO_2} = 38.2 mm Hg
	Control			Hypoxia					
Duck	8	14.6	31.8	8	22.2	67.5	+52	+112	Normocapnic Pa_{O_2} = 57.2 mm Hg
Duck	11	8.2	98.0	6	18.0	85.0	+119	−14	Hypocapnic Pa_{O_2} = 38 mm Hg
Duck	9	18.8	20.0	9	19.8	15.8	+5	+129	Normocapnic Pa_{O_2} = 38–47 mm Hg
Duck	10	16.6		10	52.7		+217		Hypocapnic(?) Pa_{O_2} = 28 mm Hg
Pigeon	13	31.7		13	74.0		+133		Hypocapnic(?) Pa_{O_2} = 28 mm Hg
Chicken	16	32		16	65.6		+105		Hypocapnic(?) Pa_{O_2} = 38 mm Hg
Chicken	8	19.3	22.9	8	26.3	47.4	+36	+107	Normocapnic Pa_{O_2} = 57.4 mm Hg

All data from unanesthetized animals; derived from Andersen and Løvø (6), Butler (18,19), Jones and Purves, (54), Jones and Holeton (52), Butler and Taylor (21,22). Control values obtained breathing air before exposure to hypercapnic or hypoxic gas mixtures. No. = number of animals used to establish the mean values given.

esthetized animals, particularly to hypercapnia, is depressed compared with awake or decerebrate animals (39, 55). Table 1 is provided to summarize some recent data for unanesthetized birds on changes in breathing frequency and tidal volume in response to hypercapnia and hypoxia. As can be seen from Table 1 there is considerable variation in response even within a single species but it appears that hypoxia has a greater effect on breathing rate and a somewhat lesser effect on amplitude than hypercapnia. Jones and Purves (54) showed that denervation of the carotid bodies abolished changes in $\dot{V}_E$ during hypoxia whereas the response to steady-state hypercapnia was unaffected. However, the rate at which $\dot{V}_E$ increased in response to increased CO_2 was markedly reduced, implying the dominance of arterial chemoreceptors over pulmonary receptors in the response to small transient changes in inhaled CO_2. These data also suggest that in the duck there is some form of central CO_2-sensitive area, which is supported by Artom's contention (7) that ducks respond to hypercapnia following bilateral cervical vagotomy; these data contrast with the results of recent experiments by Bamford and Jones (51), described above, showing that in the absence of vagal feedback ducks are insensitive to changes in Pa_{CO_2}. In resting chickens, carotid chemoreceptor drive appears to be slight since denervation of carotid receptors does not affect the pattern of respiration (34) but the importance of carotid chemoreceptors in governing the breathing frequency response to hypoxia can be assessed from Butler's work (18) demonstrating that bilateral cervical vagotomy destroyed the response. Also, intravenous cyanide injections in hens cause increases in afferent chemoreceptor discharges recorded from vagal slips and in ventilation (16).

The respiratory responses to hypoxia and probably hypercapnia are undoubtedly dependent on an arterial chemoreceptor contribution that apneic asphyxia should enhance (16, 54). Certainly the integrity of carotid body chemoreceptors has been shown to be necessary for full expression of the cardiovascular responses to submergence (44, 45, 53). Obviously chemoreceptor discharge during a dive must be either ignored by the central respiratory neurons or prevented from impinging on them. A more complex possibility is that chemoreceptor sensitivity to changes in blood gas tensions is reduced during apnea so that while input is sufficient to initiate the cardiovascular response, the susceptibility to which must be enhanced, it is not sufficient to stimulate breathing in the face of powerful inhibitory mechanisms. It is known from mammalian studies that changes in Pa_{CO_2}, pH, level of circulating catecholamines, blood flow, cervical sympathetic activity, and sinus nerve efferent activity may alter the sensitivity of arterial chemoreceptors to Pa_{O_2}. In ducks, however, there appears to be little effect of apnea per se on receptor sensitivity since the discharge frequency at a given level of Pa_{O_2} is very similar to that observed at the same level of Pa_{O_2} induced by presenting the respired animal with hypoxic gas mixtures (11). Chemoreceptor discharge increases markedly during apnea with a time course roughly paralleling that of the cardiac chronotropic response, so that maximum discharge frequency corresponds with the greatest bradycardia. This response in ducks is quite unlike that seen in the muskrat in which chemoreceptor discharge—integrated over set time periods—is immediately reduced when water flows through the nose compared with the control (pre-water) situation (Drummond, Jones and Purves, unpublished). In muskrats the cardiac chronotropic response can be reflexly evoked by nasal stimulation with water whereas in ducks it follows as a consequence of apnea (20, 28), which may explain the difference between these two divers in terms of chemoreceptor output in the initial stages of the dive, for in ducks diving bradycardia is brought about by increased chemoreceptor discharge. But the maintenance of diving apnea in ducks is certainly not a function of reduced chemoreceptor sensitivity so this normally important input for respiratory stimulation must be either ignored or prevented from impinging on the central respiratory neurones.

SUMMARY

Avian respiratory pacemaker activity is dependent on some form of peripheral input but it may be inhibited by both central and peripheral stimulation. At present the results of central nervous stimulation are difficult to interpret but, aside from cortical influences, diving apnea appears to be maintained, in the face of increasing chemoreceptor input, by noxious stimulation of the upper respiratory tract and depression of the output of medullary respiratory neurons by advancing hypercapnia. If this is so, an obvious problem for future research is what initiates the prompt onset of hyperpnea when the animal surfaces and breathes. It is known that post-dive hyperpnea is little affected by either carotid body or pulmonary denervation, so peripheral chemoreceptors are unlikely to play a major role in this response.

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