Reflexes from the lungs and airways: historical perspective

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Widdicombe, John. Reflexes from the lungs and airways: historical perspective. J Appl Physiol 101: 628–634, 2006; doi:10.1152/japplphysiol.00155.2006.—Historical aspects of respiratory reflexes from the lungs and airways are reviewed, up until about 10 yr ago. For most of the 19th century, the possible reflex inputs into the “respiratory center,” the position of which had been identified, were very speculative. There was little concept of reflex control of the pattern of breathing. Then, in 1868, Breuer published his paper on “The self-steering of respiration via the Nervus Vagus.” For the first time this established the role of vagal inflation and deflation reflexes in determining the pattern of breathing. Head later extended Breuer’s work, and Kratschmer laid a similar basis for reflexes from the nose and larynx. Then, 50–60 yr later, the development of the thermionic valve and the oscilloscope allowed recording action potentials from single nerve fibers in the vagus. In 1933, Adrian showed that slowly adapting pulmonary stretch receptors were responsible for the inflation reflex. Later, Knowlton and Larrabee described rapidly adapting receptors and showed that they mediated deep augmented breaths and the deflation reflex. Still later, it was established that rapidly adapting receptors were, at least in part, responsible for cough. In 1954, Paintal began his study of C-fiber receptors (J receptors), work greatly extended by the Coleridges. Since ~10 yr ago, when the field of this review stops, there has been an explosion of research on lung and airway receptors, many aspects of which are dealt with in other papers in this series.

THE 19TH CENTURY

In the 2nd century AD, Galen had established, by observations on living animals and decapitated criminals, that breathing was controlled from the base of the brain (52, 71). But it was only in the 19th century that the role of reflex inputs to the brain stem began to be considered. This was after the studies of Lorry (49), Legallois (48), and Flourens (25), which established that the “respiratory center” was located in the caudal brain stem. Two types of observation were made: the effect on breathing of cutting various nerves, such as the vagi, and the results of electrical stimulation of the same nerves. These were the days before tracheostomy and anesthesia, and most of the results were rightly ascribed to changes in the larynx. By the mid-19th century, far more was known about the control of the larynx than about the control of breathing. For example, Legallois (48) showed that vagotomy or recurrent laryngeal nerve section usually led to death from asphyxia, especially in guinea pigs, and that this death was due to closure of the larynx.

Faraday’s development of the induction coil allowed controlled electrical stimulation of nerves and an acceleration of research. But the patterns of respiratory response to electrical stimulation of the vagus, recurrent laryngeal, and trigeminal nerves did not give consistent changes in breathing, possibly because the larynx was usually in place and its changes in caliber dominated the total respiratory response. Then, in the 1830s, Marshall Hall (31, 32) entered the arena; he proposed that breathing was driven by intrapulmonary CO₂, although other nerves, especially those from the larynx, had an important afferent input. The respiratory center in the brain stem was driven by “excitor nerves” and would be silent without this input. There seems to be little evidence to support his view, although, at the time, it was very influential. It seems to be based less on his own experimental observations than on an earlier study by Faraday (24), who showed that hyperventilation prolonged breath-holding time, which Hall (33) interpreted, as meaning that low CO₂ in the lungs removed a powerful stimulus to breathing. Hall’s hypothesis may be mainly of interest now because it was almost the first step on the pathway in search of pulmonary chemoreceptors, a snark that is still being hunted.

Paul Bert (4) showed that electrical stimulation of the vagi inhibited breathing. Then Rosenthal (64) found the exact opposite: that vagal stimulation caused inspiratory muscle contraction. This fitted with Hall’s concepts, although Rosenthal attributed the vagal excitatory influence to a mechanical rather than a chemical input from the lungs. There was a raging controversy that largely missed the point: although with normal breathing lung reflexes did not stop breathing, could they determine the pattern of breathing, and if so how?
Thus, in the mid-19th century, it was known that breathing was controlled from the brain stem, that there was a sophisticated sensory and motor control of the larynx, and that activity in afferent fibers in the vagi, laryngeal, trigeminal, and other nerves could interrupt breathing. But there was little concept of vagal reflexes determining the pattern of breathing. Then along came Josef Breuer.

Josef Breuer. Breuer was a clinical student who took a year off to do research in the Military Akademy in Vienna, in the department run by Ewald Hering. At the end of that year he published an abstract (9) and a single paper, “The self-steering of respiration via the Nervus Vagus” (10) (Fig. 1) [translated into English by Ullmann (11) with an excellent commentary (73)]; he then went back to his clinical studies and became a psychiatrist and the cofounder (or founder, according to Sigmund Freud) of psychoanalysis. His contribution to physiology is so important that we can forgive him his later transgressions.

Breuer’s great methodological advance was to use natural stimuli, inflation and deflation of the lungs, rather than electric stimulation and section of nerves. He showed that “expansion of the lungs reflexly inhibits inspiration and promotes expiration, the more strongly the greater expansion” (Fig. 1); “Reduction in lung volume arrests instantly any expiratory movement that may be in progress at the time, and at once elicits an inspiration”; “All these manifestations disappear with section of the vagi” (Fig. 1). The Hering-Breuer inflation and deflation reflexes had been identified.

Breuer recognized that the deflation reflex could be due to lessening of activity in the pathway for the inflation reflex, so that one pathway could mediate both reflexes, a view advocated by Gad (27). Breuer said that he intended to do experiments to test this possibility, but he never did them or they were never published. It was a problem that Head solved later.

Breuer did many other experiments on the lung reflexes, sophisticated for the time, but there is no space to itemize them here, save two. In 1667, Hooke (37) showed that, if the lungs of an open-chest dog were inflated by maintained airflow passing through perforations in the pleura, breathing was arrested. Gad (27) used this experiment to justify his belief in pulmonary CO₂ receptors. Breuer repeated the experiment with smaller lung inflations, which slowed but did not arrest breathing, and also after vagotomy. The latter slowed breathing even more, without lung volume change (open chest). He argued that this could not be due to the inflation or deflation reflex pathways, because these had phasic volume inputs and lung volume was fixed. Also, the inflation reflex slowed breathing and its removal would cause acceleration, whereas the deflation reflex would be inactive because the lungs were inflated. He concluded cautiously that there might be a third afferent pathway from the lungs with maintained (“tonic”) activity that accelerated breathing. Had he discovered the pulmonary C-fiber reflex that Painial (58) “rediscovered” 70 yr later?

Second, Breuer described an inspiration-augmenting effect of lung inflation with intact vagi, but he disparaged the effect because it could not be consistently produced; it seems likely that he had described reflex augmented breaths or Head’s paradoxical reflex (see below).

Breuer must be regarded as the father of lung reflexology. His paper is remarkable not only for its observations but also for the way in which he stated hypotheses and went on to test them, and for the care with which he stated his conclusions. For over 20 yr, his results were hotly disputed, especially by Rosenthal (65). It was only in the 1930s with the development of single-fiber recording that Breuer’s conclusions were confirmed and established as basically sound.

Henry Head. Head was a medical student (like Breuer) at Cambridge when he went to work for 3 yr (1884–1886) with Ewald Hering, who had moved to the “German University” in Prague. Afterward, he returned to England and, neglecting respiration, became the most distinguished neurologist of his day (89). With Hering, Head set out to answer some of the questions Breuer left unanswered. His two papers (34, 35) (“Experimental” and “Theoretical”: 81 indigestible pages in one volume of J Physiol), describe two technical advances that enabled his to do so (72). He developed the technique of Gad (27) of blocking the vagus nerves by cold; this allowed repeated “vagotomies” in a single experiment and also, although Head did not know it, differential block of the nerves when they were recovering from cold. [In the 1950s, vagal reflexes were much studied by cooling the nerves to ~8°C, when myelinated but not nonmyelinated fiber conduction is blocked (19).] And Head resolved the problem that confronted Breuer and his contemporaries, that if you were studying vagal reflexes, the stimulus, lung volume change, interfered with what you were measuring (lung volume change). Head used a slip of the diaphragm, isolated from the lungs, to record inspiratory activity. (Earlier, observations of movement of the nares had been used to circumvent this problem!)

Despite 3 yr of work and a massive double publication, Head is mainly remembered for only two new observations about respiratory reflexes (84). He answered Breuer’s question as to whether the deflation reflex had a separate pathway from that of the inflation reflex; yes!, “If both lungs are allowed to collapse suddenly by puncturing the thorax a much stronger inspiratory effort is produced than if both vagi are divided and yet both operations equally remove the inhibitory stimulus normally passing up the vagi from the lungs.” Only the use of the diaphragm slip preparation allowed this conclusion. And he described the “paradoxical reflex”: the inspiratory effort due to lung inflation when the vagi were recovering from cold block. Decades later this reflex was shown to have the same vagal

Fig. 1. An original record from Breuer’s paper (10) showing intratracheal pressure (top) and blood pressure (bottom) in a dog. The record reads from right to left. Top traces show how inflation of the lungs with an increase in pressure causes a long-lasting cessation of respiratory movements and a fall in blood pressure. Bottom traces show the effects after vagotomy, with no inhibition of breathing movements.
pathway as the deflation reflex, and to mediate inspiratory efforts such as augmented breaths and gasps (46) and the first breath of newborn mammals (15).

Florian Kratschmer. Like Breuer, Kratschmer (as a just-qualified doctor) worked for a single year in Hering’s laboratory in Vienna, and he published a single paper ([43]; translated into English by Ullmann (44)]. Afterward, he had a distinguished career in public health and became the first military Professor of Public Health in Vienna (82, 89). The single paper established and detailed the mechanisms and importance of respiratory and cardiovascular reflexes from the nose and larynx. Using “natural stimuli,” again like Breuer, such as cold air, tobacco smoke, carbon dioxide, ammonia, and chloroform, he applied them to different parts of the upper airways, recorded a variety of responses, and established their nervous pathways by nerve section. To give three examples: he described the glottal closure reflex on nasal and laryngeal stimulation; the cardiovascular responses with the same stimuli [surprisingly these had not been described before (the methods, such as Marey’s tambour), for their recording was not generally available]; and the respiratory, cardiovascular and glottal components of the diving reflex. He was the first to describe cardiac arrhythmias on upper airway stimulation, recently rediscovered by researchers on pollution (20, 21).

Kratschmer’s work (44) has been rather ignored, possibly because it was first translated into English only in 2001. He did for the upper airways what Breuer and Head did for the lungs but in quite a different style. His paper is a jumble of methods, observations, and conclusions, in almost any order. There are no hypotheses. The results are given in uncompromising black and white.

Breuer, Head, and Kratschmer each published essentially a single paper, and then each moved on to great distinction in fields outside physiology. When we digest the papers, we find that Breuer offers gourmet food, Head a stodgy suet pudding containing a couple of plums, and Kratschmer a dog’s dinner; but together they provide a wonderful three-course meal.

And we must not forget Ewald Hering (the head chef). He was a distinguished scientist, but his greatest achievement must have been to have attracted two medical students and a novice-doctor and, after a total of 5 yr of work, to have helped lay the foundation of our knowledge of respiratory reflexes (89).

SINGLE-FIBER RECORDING

There were no dramatic advances in our understanding of lung reflexes until the development of recording action potentials in single vagal fibers. This demanded very sensitive amplifiers with a very rapid time response. Earlier Einthoven (22) and others had recorded electrical activity from the vagi that showed respiratory and cardiac fluctuations, using a slow and insensitive string galvanometer. But after the development of the thermionic valve and its use in wireless (now radio) in the 1920s, a valuable tool became available. The first records were with oscillographs, recording directly onto photographic paper, but this was soon replaced by the oscilloscope. This technique, now widespread in research, must have presented formidable problems to its originators.

Slowly adapting pulmonary stretch receptors. Adrian’s classic 1933 paper (1) showed action potentials in single vagal fibers from what were later called slowly adapting pulmonary stretch receptors (SARs) (Fig. 2). Their discharge depended on the degree of lung inflation, with a low-volume threshold; they were inhibited by deflation (which activated a different set of fibers), and they adapted slowly to maintained inflation. Adrian at once realized that he was analyzing the afferent pathway for the Hering-Breuer inflation reflex. Breuer had been vindicated!

Perhaps surprisingly, since Adrian’s paper there has been less interest in the reflexes from SARs than in those from other lung afferents—rapidly adapting receptors (RARs) and C-fiber and cough receptors. Different types of SARs have been described, based on adaptation rate, volume threshold and sensitivity to inflation. Those outside the lungs, for example in the trachea, have quantitatively different features to those in the pulmonary bronchi (55, 66, 68). But it is not known whether the different subtypes give rise to different reflex activities.

SARs were shown to be localized within the airway smooth muscle (45, 77), although recent work has suggested that this early picture is too simple (90); they can be sensitized or stimulated by smooth muscle contraction (66, 77). They are in general insensitive to chemical agents (compared with other lung receptors), but they are inhibited by CO₂ (66). This brings to mind Hall’s (33) belief that there was a tonic vagal drive to breathing due to lung CO₂-sensitive receptors, and that inflation lowers this drive. Reduced CO₂ in the lungs during their inflation would sensitize the SARs and promote the ending of inspiration. Whether this mechanism exists is unknown, and, if

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**Fig. 2.** Top: an original record from Adrian (1) showing lung volume change (above) and single vagal fiber activity from a slowly adapting receptor (below) in a cat. A, B, and C show increasing volumes of inflation. Bottom: an original record from Knowlton and Larrabee (41) showing intratracheal pressure (above) and recording from a slowly adapting receptor (below) in a cat.
it does, it does not justify Hall’s hypothesis because the afferent process would be quite different.

The connections of SARs in the brain stem have been mapped out. Original studies by Euler (23) suggested that they activated an inspiratory off switch, thus terminating inspiration (29). Recent studies have gone a long way to detailing the connections of SARs and other neurons in the medullary respiratory rhythm generator [e.g., Refs. 61, 69, 70; McCrimmon, this series (54)]. SARs shorten inspiration and prolong expiration. If they were the sole pulmonary reflex influence on the respiratory rhythm generator [e.g., Refs. 61, 69, 70; McCrimmon, this series (54)].

SARs have reflex actions on motor pathways other than those to the respiratory muscle. They relax the airway smooth muscle: a negative-feedback loop (86). They may have an influence on respiratory sensation and breath-holding time (29). They increase heart rate, a process that could be important in exercise (16). Interestingly, this observation was first made by Hering in 1871 (36), who established the process as a vagal reflex.

What is the advantage in controlling the pattern of breathing by lung sensors? It has been proposed that, because different patterns of breathing impose different loads on the respiratory muscles with only one pattern optimal in terms of work and force of breathing, the SARs adjust breathing pattern to this optimal value (87). The reflex relaxation of airway smooth muscle by SARs could be part of this mechanism, and it has been suggested that there is an optimal airway caliber for each pattern of breathing and that SARs help determine this caliber. But these concepts are rather speculative, and even if the mechanisms exist, their importance has not been established and has been disputed (56).

There seems to be no equivalent of SARs in the larynx, perhaps because there is no smooth muscle there. Although apneic reflexes are well described (51), these are probably mediated by C-fiber receptors. “Pressure receptors” have been identified and could be similar to SARs, but their reflex actions on breathing have not been established. They have myelinated fibers and are slowly adapting. They respond to laryngeal inflation, and some to collapse as well (51, 88). Like SARs, they are inhibited by CO₂ (8). They have not been identified histologically.

The role of SARs in controlling the pattern of breathing in humans may be minor. For the same lung inflation, adjusted for body size, the Hering-Breuer reflex is ~10 times weaker in humans than in rabbits (78), and vagal blockade with local anesthesia does not change the pattern of quiet breathing (30). It is possible that the action of SARs on bronchomuscular tone and on the cardiovascular system is more important, but this does not seem to have been tested.

RARs. RARs were first described by Keller and Loeser in 1929 (40), using an oscillograph; they concluded that they caused cough (see later) (Fig. 3); the receptors responded to lung deflation and mechanical stimuli (a catheter). Adrian (1) described deflation receptors, but did not say that they were rapidly adapting and did not discuss their reflex action, although he refers to the Keller and Loeser paper. Their first comprehensive analysis was by Knowlton and Larrabee in 1946 (41), with beautiful single-fiber records (Fig. 3). In an adjacent paper (46), they argue convincingly that they cause inspiratory efforts or augmented breaths. These are the equivalent of Head’s paradoxical reflex, but, given a stimulus of the right size and timing, one does not need partial vagal block by cold to reveal the reflex. Knowlton and Larrabee neither discuss cough nor mention the Keller and Loeser paper.

I made my own contribution to the study of RARs when, in the early 1950s, and under the superb guidance of Geoffrey Dawes, I analyzed the properties of those in the trachea and large bronchi of the cat (75, 76, 78). They were a motley collection. Depending on their site, they had different properties: some only fired during change of the stimulus (100% adaptation index) and also had an off response rather like a Pacinian corpuscle; most were stimulated by both inflation and deflation of the lungs, with irregular firing rates and various adaptation indexes, as shown by Knowlton and Larrabee; their chemosensitivity to irritant agents depended on their site, those in the lungs being most sensitive; they were concentrated at points of airway bifurcation; and they had slow-conduction velocities (Aδ-mytelinated fiber). It was concluded that they caused cough and augmented breaths, as Keller and Loeser and Knowlton and Larrabee had shown.

Morphologically RAR myelinated vagal nerve fibers connect to nonmyelinated terminals lying in and under the airway epithelium, although this latter view has recently been revised.
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(90). Other RAR terminals appear close to postcapillary venules and may be stimulated or sensitized by airway edema (5, 39). Miserocchi et al. (55) showed that stripping the epithelium of the trachea did not abolish the sensitivity of RARs, indicating that they had terminals deep to the epithelium, but the total distribution pattern of a receptor was not identified until recently. Unlike the SARs that, in most species, are restricted to the posterior wall of the trachea where there is trachealis muscle, RARs are found throughout the entire circumference (55).

The reflex actions of RARs are, as already described, cough and augmented breaths (18). This view was supported by the observation that healthy mice and ferrets, which lack airway epithelial nerves (57, 63), have no cough reflex from the lower airways (42); this may not apply to those with diseased lungs. Whether these species also lack an augmented breath reflex does not seem to have been studied. The RARs also cause reflex secretion of mucus from the lower airways (81, 83). Surprisingly, their cardiovascular reflex actions have not been delineated. They are sensitized or stimulated by mucosal edema, smooth muscle contraction, and decreases in lung compliance (39, 66, 83); the last observation led to the concept that, as lung compliance fell during quiet breathing due to lung collapse, the RARs would become more active until threshold for an augmented breath was reached and the fall in compliance would be reversed (67, 83).

The laryngeal equivalent to lung RARs is the “irritant receptor” (88). They are normally silent but are activated by (e.g.) touch, water, and cigarette smoke. They have myelinated afferent fibers and adapt rapidly to mechanical stimuli. It is assumed that they cause cough and the expiration reflex from the larynx.

C-fiber receptors. It had long been known that the majority of vagal afferent nerve fibres were nonmyelinated, but it was not until 1955 that Autar Paintal (58) began to explore them. His first records (e.g., Fig. 4) showed multifiber activity, and over a decade he showed that this could be activated by selective chemicals such as phenylbiguanide and, later, capsaicin and lobeline. He initially called them juxtapulmonary capillary receptors; he believed this was their site because they responded promptly to drugs injected into the pulmonary artery. However, the alveolar wall contains few nervous receptors (66), and they could also be in the walls of bronchioles and smaller bronchi; the name was abbreviated to type J receptors, and then to J receptors. Because similar receptors are found in the walls of the bronchi, the larynx, and the nose, they seem to be part of a widespread population of polymodal nociceptors found in most visceral and somatic tissue; they are now usually called pulmonary C-fiber receptors (13, 14).

Paintal and others (59, 60) showed that the receptors were activated by a variety of foreign chemicals, irritants, and inflammatory mediators and that they were also stimulated in a number of pathological conditions such as anaphylaxis, pneumonia, and microembolism. John and Hazel Coleridge (13, 14) greatly extended this work, and in addition identified a group of bronchial C-fiber receptors, which, in general, had sensory and reflex properties similar to the pulmonary ones, but differed in their sensitivities to various agents.

Paintal showed that the pulmonary receptors reflexly caused apnea followed by rapid, shallow breathing, bradycardia and hypotension via the vagi; later studies, especially by the Coleridges, extended the list to include bronchoconstriction, laryngospasm, airway mucous secretion, and bronchial and nasal vasodilatation (13, 50).

Paintal advocated two further reflexes from the pulmonary C-fiber receptors that have proved more controversial (38, 79). First, that they induced cough; yet in a mass of papers there is not a single example of a chemical selective for pulmonary C-fiber receptors causing cough, whether the animal is anesthetized or not, and including a variety of species from rat to monkey. Indeed the fibers have been shown to inhibit cough (72). The exception is the use of lobeline in humans; this may stimulate bronchial C-fiber receptors and give rise to an unpleasant sensation localized to the larynx and upper trachea, and it has been suggested that this sensation causes cough as a behavioral response. [A recent paper by Paintal and colleagues (62) refutes this view.] For obvious reasons, one cannot identify the receptors stimulated by lobeline in humans, and in other species it does not cause cough. There is still much controversy as to the afferent pathways for cough (78, 79, 85). Second, Paintal and colleagues established that in cats pulmonary C-fiber excitation inhibited spinal reflexes to skeletal muscle, and they proposed that this mechanism limited the duration of severe exercise. This was named the J reflex. However, a recent study in humans (28) showed that activation of the receptors had the opposite effect (increasing the strength of reflexes in the arm and leg of humans), so the issue remains controversial (80).
RECENT HISTORY

I have described how, at a time about a decade ago, we thought that there were three general types of sensory receptor in the lungs and lower airways: SARs, RARs, and C-fiber receptors. Their properties and reflex actions had been analyzed and were generally agreed. Each of these groups could be subdivided, but the roles and relative importance of the subdivisions were not usually very clear. The upper airways showed a rather similar pattern, but with additional receptor groups of receptor presumably appropriate to the different airway functions.

The last decade or so has seen an explosion in our knowledge of the receptors and their reflexes and a transformation in our understanding of their physiology. The following are some examples.

1) New receptors have been described: e.g., Aδ-nociceptors and “cough” receptors (53). Neuroepithelial bodies in the bronchial epithelium, known to have an innervation since 1949 (26), are now being studied for their reflex role [Adriaesen et al. (2, 3), this series].

2) The membrane receptors on the various sensory nerve terminals in the airways are being exhaustively investigated, especially in relation to stimuli for cough [Undem and colleagues (47, 74), this series].

3) The plasticity of the receptors, at peripheral, ganglionic, and brain stem level, has been established and intensively studied [Bonham (6, 7), 12 this series]; the results are having great significance in applying physiological studies to disease.

4) The complex brain stem pathways for the reflexes are being precisely delineated [61, 69, 70, McCrimmon (54), this series], together with their connections to the cerebral cortex where the voluntary control of cough is localized.

These novel aspects of lung and airway reflexes are outside the scope of this Historical Perspective, but many are considered in the other contributions to this series.

If there were a Josef Breuer Prize for research into respiratory reflexes, which there should be, the last few years would offer an embarrassing de richesée of young (and not so young) claimants for the award.

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REFERENCES


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51. Paintal AS. Impulses in vagal afferent fibres from specific pulmonary deformation receptors. The response of these receptors to phenyl diguanide, potato starch, 5-hydroxytryptamine and nicotine, and their role in respiratory and cardiovascular reflexes. QJ Exp Physiol 40: 89–111, 1955.


