Cough: Pathophysiology, Diagnosis and Treatment

Alessandro Zanasi
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To John G. Widdicombe (1925–2011): You never stopped believing in research. We are all indebted to you.

Preface

Patients usually refer to the doctor complaining of a symptom but the vast majority of medical textbooks focus on diseases rather than on symptom management. Therefore, it follows that a symptom-oriented approach probably best reflects the correct patient/physician interaction in all fields of clinical medicine. Symptoms like dyspnoea, sneezing and cough are normal behavioural responses brought about by changes in the physiological *milieu* of the respiratory tract. These symptoms are not pathological conditions *per se*, as they may be in the case of pain; however, when they persist and/or are troublesome, they may become intolerable and result in severe worsening of the patient's quality of life.

Chronic cough, that is a cough lasting longer than eight weeks, is among the most common respiratory symptoms for which patients seek medical advice. It has long been recognised that virtually all diseases of the respiratory tract, and some non-respiratory disorders, are accompanied by chronic cough, and that a relevant percentage of individuals may suffer from a long-lasting cough for which no respiratory or extra-respiratory cause can be identified. While in the first instance treatment of the underlying cause almost invariably results in cough disappearance, in the case of a cough of unknown origin, management often fails, and patients are left with a chronic condition severely affecting their everyday life. These patients are currently believed to be affected by a condition known as the "cough hypersensitivity syndrome" (CHS), in which the physiological cough reflex becomes hypersensitised to stimuli that are innocuous to the normal population. The hypersensitisation mechanisms are still poorly defined and may implicate both peripheral and central (medullary) neural structures that are crucial for the production of the cough motor pattern and potentially represent a strategic site of action for antitussive drugs. One of the main reasons for treatment failure in patients with CHS is that doctors do not try to suppress a fundamental defensive reflex mechanism, thus causing obvious detrimental effects. Rather, they try to control the *excess* coughing while maintaining a normally functioning defensive response. This attempt has been the object of recent physiological, pathophysiological and pharmacological research, the most significant advancements of which are dealt with in this book. Indeed, investigations on the basic physiological and pathophysiological mechanisms underlying cough could lead to novel therapeutic approaches.

This book also provides an updated and comprehensive overview of the new perspectives for clinical management of patients with chronic cough. It enables

readers to gain an in-depth understanding of the diagnostic workup of cough, still one of the most frequent and challenging symptoms in daily medical practice. The most common causes of chronic cough (asthma, postnasal drip, gastro-oesophageal reflux and chronic hypersensitivity syndrome) are also explored as well as the different types of paediatric cough.

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Part I

Cough Sensorymotor Mechanisms

Physiology of the Cough Reflex: Sensory and Mechanical Features

1

Donatella Mutolo, Ludovica Iovino, Elenia Cinelli, Fulvia Bongianni, and Tito Pantaleo

1.1 General Features

Cough is one of the most important airway defensive act aimed at removing foreign particles or endogenously produced materials from airways and serves as a vital defensive mechanism for lung health [1, 2]. It can be an adequate reflex in response to nociceptive stimuli applied to the airways, i.e., stimuli that may actually or potentially damage tissues (e.g., [3, 4]), but can also be voluntary or behavioral. The cough reflex involves the activation of one or more subsets of airway afferent fibers. The importance of an intact cough mechanism is reflected in the occurrence of pulmonary problems when cough is inefficient. Noticeably, cough is the most common symptom for which patients consult a doctor. Cough reflex is purposeful and useful under many circumstances ("appropriate cough"), but is without an apparent benefit or even with clear physical and psychological complications in cases of persistent or chronic cough ("inappropriate cough"). This latter greatly decreases patient's quality of life and may lead to secondary damage of the airway wall and ribcage. Antitussive drugs possess scanty efficacy, and their use is limited by severe side effects. Therefore, further research is necessary for a better understanding of the neural mechanisms involved in acute and chronic cough and to find reliable treatments [5]. However, it seems important to note that not only upregulation but also downregulation of airway defensive reflexes is of clinical interest. In particular, an impairment of airway protective reflexes, including cough and swallowing, in some neurodegenerative diseases (e.g., Parkinsonism, Alzheimer's disease, fronto-temporal dementia) or following ictus could lead to

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high risk of aspiration and pulmonary infections with consequent life-threatening conditions (e.g., [5–9]). Studies on animal models of chronic cough or neurodegenerative diseases could be most appropriate to disclose novel therapeutic approaches. Nevertheless, also investigations on the basic neural mechanisms subserving the cough reflex performed on healthy preparations can provide useful hints for further cough researches and for the development of antitussive or protussive therapies (see, e.g., [7, 10]).

It is important to point out that, despite some differences, cough displays very similar mechanical and airflow features when produced reflexly or under voluntary control [11, 12]. Cough is produced by complex and sequential changes in several upper airway and chest wall muscles. These muscles are responsible for normal eucapnic breathing and their activity depicts a respiratory cycle divided into three phases: inspiration, postinspiration, and expiration (see, e.g., [13]). Similarly, cough that consists mainly of a modified respiratory act (e.g., [1, 14]) includes at least three phases: inspiratory or preparatory, postinspiratory or compressive (glottal closure), and expiratory or expulsive (see also below). A fourth cessation phase has also been described. Both mechanical and chemical perturbations within the airways can evoke coughing bringing into action cough-related afferents that elicit coughing either by reflexively reconfiguring the brainstem respiratory network or via ascending pathways to the cerebral cortex to produce perceivable sensations associated with airway irritation that promote irrepressible coughing (behavioral cough; see Chap. 3 in this book). In fact, a characteristic aspect of human cough motor responses in both acute and chronic conditions is the "urge-to-cough" caused by a tickling sensation in the upper airways that leads to behavioral coughing [15, 16]. Reflex and voluntary cough present similarities, but also different features. In addition, the cough reflex is under a high degree of voluntary control that can modulate its expression up to complete suppression [11, 12, 17–19].

The contribution of higher brain structures to the control of the cough reflex is also clearly reflected in its relationship with sleep and anesthesia. This reflex very strongly depends on the sleep-wakefulness state. In dogs, laryngeal or tracheobronchial stimulation causes coughing during awakefulness, but not during slow-wave sleep (SWS) or rapid-eye-movement (REM) sleep. Only when the intensity of tussigenic stimuli becomes sufficient to induce arousal, the cough reflex develops, i.e., it always follows arousal. The intensity of laryngeal stimulation required to produce arousal and coughing is higher in REM sleep than in SWS [20, 21]. Other reflexes of laryngeal origin (apnea, bradycardia, expiration reflex) can be evoked without arousal. This suggests that only the cough reflex relies on supra-medullary neural processes active only during wakefulness. Similarly, anesthesia deeply affects respiratory reflex responses to stimulation of the tracheobronchial tree. For instance, under the highest levels of anesthesia, the patients do not cough, rather they respond with a prompt apnea. On the other hand, the cough reflex is progressively more frequent by reducing the level of anesthesia, while the apneic response shows an opposite trend [22].

1.2 Cough-Related Afferents

Reflex cough is mediated by vagal afferents from the upper airways and the tracheobronchial tree [19, 23, 24]. Also some other extrarespiratory sources of cough are supplied by vagal afferents, such as the external acoustic meatus (auricular branch of the vagus nerve, Arnold's or Alderman's nerve) that mediates the Arnold's ear-cough reflex [25–27]. Other tussigenic areas may be the visceral pleura and the esophagus (for review see [28]). Gastroesophageal reflux seems to be a factor in some airway disorders associated with cough and bronchoconstriction [29–31].

1.2.1 Tracheobronchial Tree

The general characteristics of airway vagal afferent neurons, mainly derived from studies in cats and rodents (guinea pigs, rats and mice), have been extensively reviewed by Sant'Ambrogio and Widdicombe [32], Lee and Yu [28], and Mazzone and Undem [19]. The cell bodies of vagal sensory fibers innervating the respiratory tract arise from two distinct ganglia, i.e., the nodose ganglion and the jugular ganglion, and have their first central station in the nucleus tractus solitarii (NTS). The nodose and jugular afferent fibers differ in several characteristics, including distinct molecular phenotypes, peripheral distribution to the tracheobronchial tree, and projections to brainstem structures (see [19]). Sensory nerve terminals can be found widely distributed throughout all the levels of the airway tree and in association with the various tissue types of the airway wall and with different end-organs. Afferent receptors described as present within the tracheobronchial tree and lung parenchyma are divided into three broad classes: slowly adapting stretch receptors (SARs), rapidly adapting stretch receptors (RARs), and bronchial and pulmonary endings of C-fibers. There are, in addition, slow adapting nociceptors innervated by Aδ and C fibers and the polymodal neuroepithelial bodies. However, their involvement in the cough reflex is at present obscure. Some important features of these receptors have been reported in several reviews [19, 25, 32–34]. This classification is based on a variety of properties such as adaptation during sustained lung inflations and conduction velocity of related afferent fibers. The main receptors implicated in the cough reflex are SARs, RARs, and bronchial and pulmonary C-fibers.

Cough-related receptors mainly located in the large extrapulmonary airways (trachea, carina, main bronchi) belong to the wide family of pulmonary RARs innervated by Aδ fibers, possibly including the so-called "cough receptors" described in the guinea pig larynx and rostral trachea [35–37]. RARs are a heterogeneous family of polymodal receptors and some of them are particularly sensitive to various kind of mechanical stimuli of the airway mucosa or airway muscular walls (rapid inflation and, especially, deflation) and to chemical irritant stimuli, such as citric acid, ammonia, and cigarette smoke, as well as to hyper- or hypoosmotic solutions (e.g., distilled water, mainly because of a lack of permeant anions, in particular chloride). Activation of RARs in the deep intrapulmonary airways usually

provokes hyperpnea/tachypnea, augmented breaths, bronchoconstriction, laryngeal closure, but very rarely cough. Further evidence for their role in coughing comes from studies of vagal cooling, which blocks cough at temperatures that selectively abolish activity in myelinated fibers (including Aδ afferent fibers from RARs) while preserving C-fiber activity [34, 38].

The abovementioned "cough receptors" described in guinea pigs [35–37] are innervated by slowly conducting Aδ-fibers that arise from nodose ganglia. They are sensitive to punctate mechanical stimuli of the epithelium overlying the sensory endings, and to rapid changes in luminal pH (acidification) or to hypotonic solutions (e.g., distilled water) due to the expression of acid sensing ion channels (ASICs) and Ca^{++}-activated chloride channels, respectively. However, they are unresponsive to capsaicin, bradykinin or hypertonic saline, smooth muscle contraction, and changes in airway luminal pressure. Furthermore, the "cough receptors" possess stimulus specificity. For example, ATP activates RARs, but not Aδ nodose fibers, and is relatively ineffective at evoking cough in anesthetized animals (for further details see [19]). Like other mechanosensors in the lung, a single myelinated axon can give rise to one or several unmyelinated arborized terminals that lay above the airway smooth muscle, but below the epithelium basement membrane. This location for cough receptor terminations may explain their relative insensitivity to airway smooth muscle contractions [19, 25]. Like Aδ RARs, they do not express transient receptor potential vanilloid type 1 (TRPV1) channels under normal healthy conditions, but only when airway inflammation is present. Recent results on the antitussive effects of long-acting muscarinic receptor antagonists (LAMAs) are consistent with the possible role of this type of receptors in cough production both in awake and anesthetized rabbits [10, 39]. However, their presence in the tracheobronchial tree of this animal species remains to be ascertained. The results of these studies strongly suggest that other membrane receptors, in addition to the TRPV1 channels, as shown by Birrell et al. [40] in guinea pig, should be taken into consideration in the mediation of LAMA antitussive effects, such as ASICs and mechanoreceptors of cough-related afferents.

SARs, corresponding to a great extent to pulmonary stretch receptors, are highly sensitive to lung inflation and are the primary afferent fibers involved in the Breuer-Hering inflation reflex, which terminates inspiration and initiates expiration when the lungs are sufficiently inflated. Their activity increases during inspiration, reaching a maximum just prior to the beginning of expiration. SARs are primarily associated with smooth muscle in the tracheobronchial tree. They may have a permissive role in the cough reflex (absence of cough reflex responses when they are selectively blocked) only in some animal models, e.g., in rabbits, but not in dogs (see, e.g., [41–43]). Their action may be due to their facilitatory influences on expiratory motoneurons and, therefore, on the reflex activation of expiratory muscles during coughing [24, 32, 44]. Interestingly, other studies in guinea pigs found no evidence for a permissive effect of SARs in cough production [45]. Admittedly, the role of pulmonary stretch receptors and, in particular, of volume-related feedback in the regulation of the cough reflex is controversial [46–49]. Recently, Poliacek et al. [50] have reported that modified lung inflations during coughing and/or additional

expiratory airflow resistances in the cat alter the spatiotemporal characteristics of the cough motor pattern through volume-related feedback mechanisms similar to those operating during eupneic breathing. They also have suggested a significant contribution of both SARs and RARs in shaping the cough reflex.

The majority (80%) of bronchopulmonary vagal afferent nerves are unmyelinated C-fibers and cough-related afferents may originate from bronchopulmonary C-fiber endings; their sensory neurons are located both in nodose and in jugular ganglia [24, 25, 37, 45, 51–56]. Vagal afferent C-fibers are distinguished from lung stretch receptor afferents (SAR afferents) not only for their conduction velocity (<2 m/s) but also by their relative insensitivity to mechanical stimulation and lung inflation. C-fiber endings are further differentiated from lung stretch receptors by their direct sensitivity to bradykinin and activators of both the TRPV1 channels (e.g., capsaicin and protons) and the transient receptor potential ankyrin 1 (TRPA1) channels (e.g., ozone and allyl isothiocyanate). C-fiber stimulation (e.g., capsaicin inhalation) has consistently failed to evoke coughing in anesthetized animals. In addition, the cough reflex can be inhibited owing to the activation of a subset of pulmonary C-fibers in dogs, cats, and guinea pigs ([25, 38, 42, 45, 51, 57, 58]; see also [19]). The same is true for stimulation of bronchial C-fibers in dogs [38, 58]. In particular, it has been reported that cough is abolished during apnea, i.e., the initial phase of the pulmonary chemoreflex due to C-fiber receptor stimulation, and significantly reduced during the rapid shallow breathing that immediately follows apnea. These respiratory effects were accompanied by marked bradycardia and hypotension. However, at variance with previous findings, Mutolo et al. [59] have shown that tracheobronchial cough is not significantly reduced in the rabbit during the pulmonary chemoreflex, thus suggesting that species differences should be taken into consideration. Further support for the inhibitory role of vagal C-fibers on mechanically induced cough in anesthetized cats has recently been derived from the study by Simera et al. [60]. However, some studies have suggested that in anesthetized guinea pigs [61, 62] C-fiber activation does not evoke cough, but consistently reduces the threshold for coughing evoked by other receptors sensitive to both electrical and mechanical stimuli. All these findings indicate that C-fibers may be especially relevant to coughing associated with airway inflammation and inhalation of environmental irritants.

In conclusion, the role of bronchopulmonary C-fibers in the cough reflex has been the subject of considerable debate ([19]; see also [63]). Bronchopulmonary C-fibers represent a very wide family, and different subtypes have been described in different animal species (e.g., [56, 64]). In guinea pigs, C-fiber subtypes may have different origin (nodose vs. jugular ganglia), sites of peripheral airway termination (extra- vs. intrapulmonary), expression of neurokinins, and responsiveness to some neuroactive agents such as adenosine, 5-HT_3 receptor, and ATP/$P2X_{2/3}$ receptor agonists [56, 65, 66]. Recently, in agreement with previous results, it has been reported that airway C-fibers arising from the jugular ganglion initiate or sensitize the cough reflex, and that the intrapulmonary C-fibers arising from the nodose ganglion inhibit cough induced by citric acid and electrical stimulation in anesthetized animals or by capsaicin in awake animals [63]. It is unclear whether the C-fiber subtypes with

opposing effects on cough in species other than the guinea pig also arise from distinct vagal ganglia ([63] also for further Refs.). In the light of the present knowledge on the role of sensory afferents from the respiratory tract, it seems conceivable that Aδ cough-related afferents are mainly involved in the production of the cough reflex, while C-fiber cough-related afferents are mainly implicated in the generation of airway sensations, such as, for instance, chest pain, dyspnea, and the "urge-to-cough," that is characteristic of awake animals and humans and may lead to the behavioral act of coughing (see also [19, 39]).

1.2.2 Larynx

In this context, it is important to mention that laryngeal receptors are a very important source of airway defensive reflexes and, in particular, of the cough reflex [28, 44]. The main source of afferent laryngeal fibers is the internal branch of the superior laryngeal nerve. The cell bodies of these laryngeal afferents are located in the two vagal sensory ganglia, with a majority of them in the nodose ganglion. Recordings from the peripheral stump of the superior laryngeal nerve in animals spontaneously breathing through their upper airway show the presence of afferent activity with marked respiratory modulation. This respiration-related activity derives from different types of receptors: (1) receptors activated by the inspiratory cooling of the laryngeal lumen ("cold" or "flow" receptors); (2) receptors detecting either negative or positive transmural pressure in the larynx ("pressure" receptors); and (3) receptors stimulated by the contracting intrinsic laryngeal muscles and by passive movements of the larynx ("drive" receptors). Cough-related laryngeal receptors apparently display analogies with the RARs located in the tracheobronchial tree ([1, 14, 32, 34, 44] also for further details). Cough-related laryngeal receptors innervated by myelinated Aδ fibers are activated by mechanical and chemical stimuli and are often called "irritant receptors." They possibly include the "cough receptors" described above. A large proportion of "irritant" receptors responds to water or water isosmotic solutions lacking chloride ions. C-fiber activation has also been reported to have a role in cough production and it seems plausible that specific second-order neurons for cough-related laryngeal afferents exist. In this regard, Widdicombe [34] proposed a putative model of the central pathways for the cough reflex where laryngeal RARs project to their own laryngeal relay NTS neurons that have separate connections with the cough generating mechanism in the brainstem. Although the central pathways have not been investigated in detail, they are probably similar to those displayed by tracheobronchial cough afferents ([67–70]; see Chap. 3 in this book). In addition, "irritant" receptors may evoke other airway protective reflexes such as glottal closure, apnea, bronchoconstriction, mucus secretion, the expiration reflex and the swallowing reflex as well as various cardiovascular reflexes [1, 14, 19, 32, 71–73]. The expiration reflex closely resembles cough responses, but it consists of a pure expiratory effort evoked by the mechanical stimulation of the vocal fold mucosa in the absence of a preparatory inspiratory phase [1, 32, 74]. The expiration reflex can be also evoked by the

stimulation of the tracheobronchial tree [75–77]. Glottal closure and the expiration reflex can be regarded as the first level of airway defense since they prevent penetration of foreign bodies into the airways. The other laryngeal receptor afferents mediate different respiratory reflexes (see, e.g., [14, 44]). For further details on cough peripheral afferent pathways and related cough-inducing mechanisms, see Chap. 2 in this book.

1.2.3 Bronchoconstriction and Cough

Cough and bronchoconstriction are often associated. They are, however, distinct mechanisms that can be separately brought into action and differentially inhibited by drugs. Inhalation of nebulized water is well known to elicit cough and bronchoconstriction in humans. However, cough depends on a lack of permeant anions (e.g., chloride), while bronchoconstriction depends on the osmolarity of the inhaled solution. Furthermore, the effects of bronchodilating drugs on cough suggest that changes in airway tone are not involved in cough production. It is also apparent that the bronchomotor tone can be altered by inputs that do not cause cough, such as chemoreceptor stimulation and irritation of the nose or nasopharynx. Both cough and bronchoconstriction are mediated by the central nervous system, but bronchoconstriction may also be elicited by the release of mediators from afferent nerve fibers (for review see [44]).

1.3 Bronchopulmonary Sympathetic Afferents

Sensory information generated by mechanical and chemical stimuli applied to the airways and lungs is also conveyed by sympathetic afferents to the central nervous system (for review see [28]). It is generally believed that sympathetic afferents are less important than their vagal counterparts since most of the known airway reflexes can be essentially suppressed by bilateral vagotomy. However, possible interactions between these two afferent systems should be considered. In general, sympathetic afferents travel in association with sympathetic efferent fibers. Their cell bodies are located in the dorsal root ganglia and reach the paravertebral ganglia and the prevertebral ganglia through the white ramus communicans. Bronchi and lungs are supplied by fibers derived from the middle cervical ganglia, the stellate ganglia, and the upper thoracic ganglia. Central pathways may terminate at thoracic segments T1-T6 and also up to C7 and down to T8. Part of neurons in the dorsal root ganglia may contain TRPV1 and substance P. So far, sympathetic sensory receptors have not been divided into different categories. They are a heterogeneous group sensitive to mechanical stimuli (e.g., lung hyperinflation) and chemical stimuli (e.g., ammonia and smoke) and comprise polymodal nociceptive receptors. Their stimulation alters the breathing pattern in vagotomized animals. For example, bradykinin injected into the bronchial artery evokes sustained inspiration, while injected into the right atrium stimulates breathing, and applied to the lung parenchyma produces marked

respiratory excitation or inhibition as well as bradycardia and hypotension. Noticeably, both vagal and sympathetic afferents contain both TRPV1 and substance P. Sympathetic afferents contribute with vagal afferents to the genesis of respiratory sensations, especially pain arising from the pleural region [78]. The viscerosomatic and visceroviscerall convergence is probably relevant to cardiopulmonary reflexes and to chest pain originating from trachea and lower airways. It may be involved in reciprocal phenomena of sensitization (e.g., noxious damage and related pain in one organ may influence pain threshold and associated pathological responses in the other). Respiratory sensations such as dyspnea, air hunger, airway irritation, and "urge-to-cough" are generated by sensory signals arising from peripheral and central chemoreceptors or from respiratory structures, including airways, lungs, and chest wall. In particular, not only vagal afferents but also sympathetic afferents may contribute to these respiratory sensations.

It seems appropriate to recall that the solitary tract neurons receive the converging input of both somatic skeletomuscular (small myelinated and unmyelinated fibers) and vagal afferents, thus indicating that they are involved in the mediation of somatosympathetic reflexes. This viscerosomatic convergence may be the anatomical substrate of cardiorespiratory responses to muscle activity [79–82] and of central sensitization phenomena.

1.4 Respiratory Muscles

As already mentioned, the same muscles engaged during eucapnic breathing also participate in the cough motor pattern. Respiratory muscles are involved not only in lung ventilation, but also in other functions such as postural adjustments, movements of the trunk, expulsive maneuvers (cough, sneezing, emesis, defecation) and behavioral functions (sniffing, speech, and vocalization). Respiratory muscles that are similar to the other skeletal muscles comprise "pump" muscles that are responsible of inspiratory and expiratory activity and determine lung inflation and deflation, respectively. During quiet breathing the diaphragm, the parasternal intercostals, scalene (always in humans), and probably part of the external intercostal muscles produce active inspiration. Under the same conditions, expiratory muscles are generally silent, i.e., expiration is a prevailing passive event. During increased ventilation, for instance because of exercise, hypercapnia or hypoxemia, also other respiratory muscles are recruited, such as all the intercostals as well as abdominals, scalene, sternocleidomastoids, erector spinae, trapezius muscles, pectoralis muscles and other accessory muscles, including for instance those of the upper airways (for details see below).

The diaphragm is innervated by the two phrenic nerves that originate from C_3, C_4, and C_5 roots. It is anatomically unique among skeletal muscles in that it separates two body cavities and its muscle fibers radiate from a central tendinous structure to insert peripherally into skeletal structures. Diaphragm contraction produces very complex actions. The dome of the diaphragm descends relative to the costal insertions of the muscle and expands the thoracic cavity along its craniocaudal axis.

Hence, pleural pressure falls and depending on whether the airways are open or closed, lung volume increases or alveolar pressure decreases. Furthermore, it causes a caudal displacement of the abdominal viscera and an increase in abdominal pressure which, in turn, pushes the ventral abdominal wall outwards and contributes to rise the lower rib cage, i.e., that located in the "apposition zone" between the diaphragm and thoracic wall. In addition, owing to its insertion on the lower six ribs and the cranial orientation of its fibers, it lifts and rotates them outward, thus increasing the thoracic volume. As a result of the contraction of the diaphragm, the thoracic pressure decreases with a possible inward movement of the sternal portion of the thoracic wall, which however is counteracted by the activity of the parasternal intercostals.

In the electromyographic (EMG) activity of the diaphragm as well as in the electroneurogram of the phrenic nerve (but not in the EMG of intercostal inspiratory muscles) after the end of inspiration (marked by the change in the direction of the airflow), there is a short period of silence followed by a resumption of inspiratory activity during expiration. This diaphragmatic activity is called "postinspiratory inspiratory activity" or more simply "postinspiratory activity" and allows to recognize three phases in respiratory activity (Fig. 1.1), i.e., inspiration, postinspiration or E1 phase, and expiration or E2 phase characterized by the possible appearance of expiratory activity and therefore also called "active expiration" [13]. This triphasic feature can also be recognized in the organization of the central pattern generating mechanisms (for review see, e.g., [13, 83–85]). Postinspiratory activity provides a mechanism to mechanically brake the expiratory airflow and comprises glottal closure due to the activation of vocal fold adductor muscles innervated by the inferior or recurrent branches of the vagal nerves (see Fig. 1.1). This phase is of great importance for the mediation of various protective reflexes, such as glottal closure, sneeze,

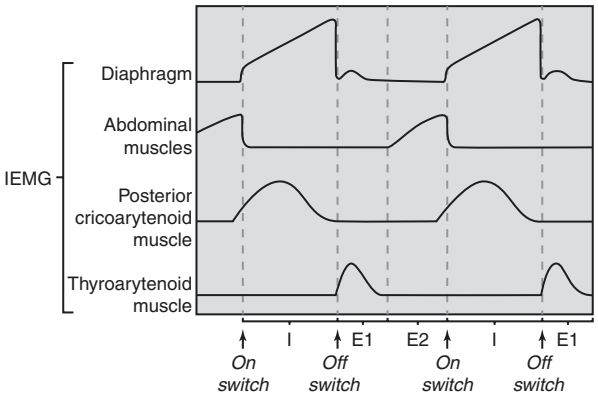

Fig. 1.1 Diagrammatical representation of the three phases of the respiratory cycle, depicted by the integrated electromyographic activity (IEMG) of the diaphragm, abdominal muscles, and thyroarytenoid muscle (larynx adductor). The activity of the posterior cricoarytenoid muscle (larynx abductor) has also been reported. *I* inspiratory phase, *E1* expiratory phase 1 or postinspiratory phase, *E2* expiratory phase 2 or active expiration

cough, and swallowing, that ensure protection against penetration of potentially harmful foreign substances into the airways [8, 86].

The diaphragm can be actually considered composed of two distinct muscles: the sternocostal and the crural or lumbar portion, respectively. These two portions have different embryonic origin and innervation, a different number of slow fibers (higher in the crural portion), different actions on the thoracic wall, and, in addition, differential activation in some motor behaviors that require a separate control of the esophageal hiatus (expulsion phase of vomiting, swallowing, belching). For instance, during the expulsion phase of vomiting, crural fibers that surround the esophagus are silent, while sternocostal fibers are active along with abdominal muscles. Proprioceptive reflexes and postural activity are poorly represented in the diaphragm. At variance with intercostals and other respiratory muscles, the diaphragm contains a few muscle spindles, which are mainly concentrated in the crural portion.

The respiratory function of intercostal muscles has been controversial throughout medical history. The theory of Hamberger (1749) deserves special mention because it provides the basis for the conventional current concepts concerning the action of intercostal muscles. He argued that external intercostals are inspiratory muscles and the internal intercostals are expiratory muscles, with the exception of the intercartilaginous (parasternal) portion which is inspiratory. According to this theory, because the fibers of external intercostals slope caudad and ventrally from the rib above to the rib below, their lower insertion is further from the center of rotation of the ribs (costovertebral articulation) than their upper insertions. When these muscle fibers contract exerting equal and opposite force at the two insertions, the torque acting on the lower rib, which tends to raise it, is greater than that acting on the upper rib, which tends to lower it. The opposite is true when the fibers of the internal intercostals contract since they slope in the opposite direction. As to the parasternal internal intercostals, they raise the ribs since their action should be referred to the sternum rather than to the vertebral column. However, for many reasons the Hamberger theory is incomplete and cannot entirely describe the action of intercostal muscles. Studies by De Troyer and coworkers in humans have shown that in the dorsal half of the second interspace the external intercostals have a large inspiratory effect, which decreases rapidly in the caudal and ventral direction [87, 88]. Thus, the effects become expiratory in the ventral half of the sixth and eighth interspaces. Furthermore, the internal intercostals have been shown to have a large expiratory effect in the ventral half of the sixth and eighth interspaces, but this effect decreases dorsally and cranially. The distribution of EMG inspiratory and expiratory activities is consistent with these results ([89]; for review see [90]). Human parasternal intercostal muscles are active during inspiration and their mechanical respiratory effect diminishes from the first to the fifth muscles with a parallel decrease in the phasic drive (EMG activity) and an increase in tonic activity [91]. During coughing, mid-thoracic external and internal intercostal muscles discharge synchronously with the diaphragm and abdominal muscles, respectively. On the contrary, both caudal external and internal intercostal muscles discharge simultaneously with abdominal muscles [92, 93]. The triangularis sterni or transversus

thoracis muscle is usually inactive during resting breathing, but contracts during voluntary and involuntary expiratory efforts, including cough. It pulls the ribs caudally and deflates the rib cage, together with the expiratory internal intercostals.

The abdominal muscles with significant respiratory function in humans are the rectus abdominis, the external oblique, the internal oblique, and the transversus abdominis. As they contract, they pull the abdominal wall inward and produce an increase in abdominal pressure. This causes the diaphragm to move cranially into the thoracic cavity with a consequent increase in pleural pressure and decrease in lung volume. These muscles, owing to their insertions on the ribs, pull the lower ribs caudally and deflate the rib cage. This action is, however, partially counteracted by the concomitant raise in abdominal pressure that exerts an inspiratory function since it expands the lower rib cage at the level of the "apposition zone."

In the upper airways there are multiple muscles at each of five major sites: the pharynx, soft palate, larynx, nose, and mouth. Their major respiratory functions are to optimize airway patency during inspiration, regulate the rate of airflow during expiration, and partition ventilation between nasal and oral routes. Among the muscles that assure the airway patency there are alae nasi muscles, that dilate the nares, the genioglossus muscle, that is the major protrusor of the tongue, the muscles that are directly or indirectly mechanically attached to the hyoid bone (geniohyoid, sternohyoid, sternothyroid, thyrohyoid muscles) which are generally believed to dilate the pharynx. Their activity precedes by a few milliseconds that of the diaphragm, reaches a maximum during the first part of the inspiratory flow, and then decreases. Laryngeal muscles produce large changes in the size and, hence, resistance of the laryngeal aperture through the inspiratory abduction and the expiratory adduction of the vocal cords. Vocal cord abduction during inspiration occurs even during quite breathing (posterior cricoarytenoid muscle contraction). Adduction of the larynx regulates the rate of airflow during expiration (relaxation of posterior cricoarytenoid muscle and contraction of adductor muscles, such as the thyroarytenoid muscle) in concert with the postinspiratory activity of the diaphragm (Fig. 1.1).

The activation of some upper airway muscles also regulates the route of airflow that, with increased ventilator demand (exercise, respiratory diseases), requires a reduction in the level of resistance and breathing occurs no more through the nose, but through the nose and mouth or only the mouth. For a more extensive account on respiratory muscle function see De Troyer and Loring [87], Sieck and Prakash [94], Duron and Rose [95], Bishop [96], van Lunteren and Dick [97], De Troyer [98], and De Troyer et al. [90]. Respiratory muscles are illustrated in Fig. 1.2.

1.5 Phases of Cough and Expiratory Flow

Cough consists of a modified respiratory act that includes three or four phases: inspiratory or preparatory, postinspiratory or compressive (glottal closure), expiratory or expulsive and phase of cessation (e.g., [1, 14, 99]). Coughing usually occurs not as a single cough, but as a succession of cough (interrupted expirations) starting

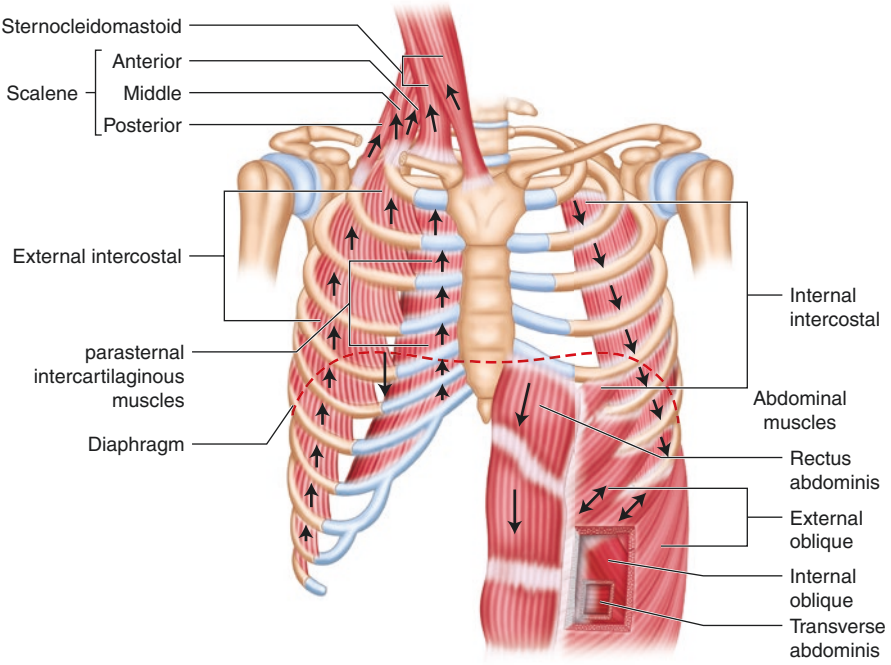

Fig. 1.2 The main inspiratory and expiratory muscles involved in coughing. (From Netter FH, Respiratory system, Publisher Ciba-Geigy Corporation)

after a deep inspiration and ending at residual volume. This pattern probably provides a better clearing mechanism in which rapidly changing swings in transmural pressure act on the wall of the tracheobronchial tree and help to loosen the mucus there accumulated.

1.5.1 Inspiratory or Preparatory Phase

Cough characteristically begins with a brief inspiration (inspiratory phase) and the opening of the glottis by contraction of the abductor muscles of the arytenoid cartilage. The volume of inspired air is variable, but usually greater than that under eucapnic breathing. The increase in lung volume may enhance the mechanical efficiency of the subsequent expiration by different means: optimization of the tension-length relationship of the expiratory muscles resulting in greater intrathoracic and abdominal pressures, and activation of pulmonary stretch receptors by lung distension leading to central facilitation of cough [100]. Although the precise mechanism responsible for the regulation of the inspired volume is not known, it should depend on the intensity of the tussigenic stimulus for reflex cough, while on the expected

forcefulness of the expiratory phase for voluntary cough. Yanagihara et al. [101] observed that when subjects were instructed to produce a single, gentle cough effort, they inspired an amount of air approximately equal to the tidal volume. When subjects were instructed to cough three times with maximal expiratory efforts, they inspired much more deeply, as much as 50% of their vital capacity [102].

1.5.2 Postinspiratory or Compressive Phase

The inspiratory phase is followed by expiration against a closed glottis (compressive phase), which produces large increases in intrapulmonary pressure. Closure of the glottis is achieved by contraction of the adductor muscles of the arytenoid cartilage. This is reinforced by apposition and displacement downward of the ventricular or false folds, except in a very gentle cough. In addition, often the epiglottis covers the laryngeal opening. The glottis remains closed for a short and variable time (often indicated as about 0.2 s) during which the abdominal, pleural, alveolar, and subglottic pressures raise rapidly, and lung volume decreases owing to the compression of alveolar gas. During the compressive phase of cough, intrapleural pressure becomes greater than atmospheric pressure, and alveolar pressure, due to the elastic recoil of the lung, will be even greater than pleural pressure. The rate and extent of the change in lung volume during this time may be surprisingly great. For example, if thoracic gas volume is initially 5 L and if intrathoracic pressure rises to 200 cmH_2O in 0.2 s, the reduction in volume due to compression is about 1 L and the mean rate of change due to compression is 5 L/s. Expiratory muscle length and contraction velocity are related to the thoracic gas volume and to the expiratory flow, respectively. Furthermore, the force-length and force-velocity relationships of the expiratory muscles are like those of other skeletal muscles. Thus, taking into considerations that force and velocity are inversely related and that in a three-dimensional structure like the thorax, force corresponds to pressure and velocity to airflow, the contractile force and therefore the intrathoracic pressure achieved would be much greater during a closed-glottis maneuver (isometric or nearly isometric conditions) than throughout an open-glottis maneuver (e.g., forced expiration). The higher pressure and the consequent higher flow presumably enhance cough effectiveness.

1.5.3 Expiratory or Expulsive Phase

The expiratory phase is the most characteristic of the reflex. The effectiveness of coughing depends essentially upon the velocity at which air flows through the airways. This depends on the total cross-sectional area of airways (i.e., velocity = airflow rate/cross-sectional area) that becomes progressively smaller from the alveoli towards the larynx. Therefore, the linear velocity of flow must be, in general, greater in large than in small airways. This phase initiates with the active opening of the glottis (abduction of the vocal folds) in 20–40 ms. The pressure in

the central airways falls abruptly towards atmospheric levels, whereas pleuric and alveolar pressures remain high or continue to rise. At the beginning, while pressure at the airway opening (mouth) remains atmospheric, pressure in the airways (alveolar level) is still greater than pleural pressure and keeps the airways distended. During air movement, intraluminal pressure decreases from the alveoli to the airway opening (due to the encountered resistances), while pleural pressure remains approximately equal throughout the intrathoracic cavity that represents the external side of all intrathoracic airways. According to the "airway dynamic compression," there must be a point along the tracheobronchial tree where pleural and intraluminal pressure are equal (equal pressure point). Upstream to this point (towards the alveoli) airways are distended, while downstream to this point (towards the mouth) airways are compressed. Thus, during this phase of coughing both trachea and main bronchi undergo considerable narrowing with corresponding increases in linear velocity of expired air, which improve the scrubbing action of this reflex. Two related but distinct events occur simultaneously. Expiratory flow from the lung periphery rises rapidly to maximal values because of the pressure gradient between alveoli and airway opening, while central intrathoracic airways abruptly collapse (due to the rapid opening of the glottis), causing volume decrements. These modest (about 100 mL) but very rapid decrements generate transient "supramaximal" flow spikes superimposed on the flow coming from the lung parenchyma and limited by the airway dynamic compression. In conclusion, the instantaneous flow through the airway opening is the sum of two flows, i.e., the expiratory flow and the transient "supramaximal" flow spikes. These events are accompanied by intense accelerations of airway wall movements and contribute to the formation and suspension of droplets. After airway collapse, there may be a phase of maintained expiration during which airway walls may flutter. All these events are of importance for airway clearance. During this phase, characteristic sounds are present with a decrementing trend, related to the intensity of airflow.

1.5.4 Cessation Phase

Cessation of cough is characterized by expiratory muscle relaxation. This sometimes occurs with the onset of (or an increase in) inspiratory muscle activity. Alveolar and pleural pressures decline towards ambient pressure. As final event, the glottis may close or on the contrary there may be a terminal expressed sound related to flow or a quiet cessation of flow with a concomitant fall of alveolar pressure to ambient pressure. For further details see, e.g., Leith et al. [99] and Sant'Ambrogio [44]. Neurophysiological and mechanical events that characterized the different phases of cough are schematically illustrated in Fig. 1.3.

Details on the cough motor pattern and the analysis of cough responses mainly derived from experiments on anesthetized cats can be found in Chap. 4 in this book.

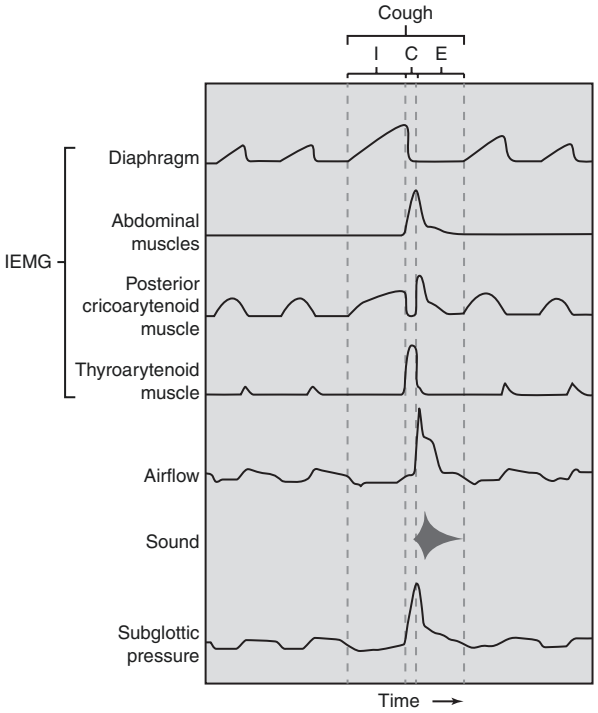

Fig. 1.3 Schematic representation of the motor pattern during a single cough along with flow at airway opening (airflow), subglottic pressure, and sound level. I, C, and E indicate inspiratory, compressive, and expiratory phases marked by vertical dashed lines. Note that laryngeal muscles are active also during eucapnic breathing and rhythmically abduct (posterior cricoarytenoid muscle) and adduct (thyroarytenoid muscle) the vocal folds. Muscle activity is reported as "integrated" electromyographic (IEMG) activity (integration of raw EMG activity is usually performed by a low-pass RC filter, time constant 100 ms)

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Sensory Pathways and Neural Modulation of Cough

2

Ivan Poliacek

2.1 Cough Afferents

Two afferent pathways are certainly involved in the initiation of cough. Both originate in the airways and both are carried out by the vagus nerve [1–4]. One is represented by A-δ fibers with the cell bodies in the nodose ganglion [5, 6] that do not express tachykinins [7]. Their peripheral endings respond to mechanical punctate stimuli, e.g., large particles present in the airways, and the rapid decrease in pH (acid) [1, 2, 5, 8–10]. The other nonspecific cough afferent pathway represents bronchopulmonary C-fibers with the cell bodies in jugular ganglion [1, 5, 6, 11] that do express the tachykinins [7, 12, 13]. C-fiber sensory terminals for initiation of cough respond to variety of stimuli such as irritants, e.g., sulfur dioxide, ammonia, cigarette smoke, exhaust, ozone, and capsaicin; neuro-stimulating chemicals mainly inflammatory mediators like nicotine, adenosine, bradykinin, and prostanoids, e.g., prostaglandin E2; and even natural molecules like water vapor, particularly hypotonic but also hypertonic solutions [2, 4, 14–24]. Cough afferents terminate on and excite the second-order neurons in the area of solitary tract nucleus of the brainstem [25–27].

The structure of sensory endings, their membrane receptors and ion channels content and their position in the airways are linked to their functional physiology [28–30]. Airway sensors are located all over the airways, those initiating cough in the larynx, trachea, and bronchi [24, 31]. In order to trigger cough, stimulating agents have to reach (affect) membrane receptors at the related terminals (sensors) of the cough afferents. A-δ sensory endings spread between the smooth muscle and the epithelial cell layers [32, 33]. C-fiber terminations locate in the airway epithelium and other structures of the airway wall [13, 33–35]. Intense depolarization at

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the sensory terminals due to the opening of membrane channels is required in order to initiate sufficient discharge of action potentials on the nerve fibers (cough receptor A-δ or cough-related C-fibers) [28, 36, 37]. It can trigger at the cough second-order neurons in the solitary tract nucleus within the brainstem the sequence of events leading to cough response [25]. Ionotropic glutamate receptors mediate afferent excitatory drive to the cough neuronal network [26, 27].

2.2 Cough Receptors

Cough receptors—mechanosensitive cough afferent endings initiate cough preventing mechanical particles to penetrate into the lower airways and cleaning the area from mechanically stimulating content, including accumulated mucus [31, 38]. According to that, the most mechanosensitive area of the airways is larynx, at least when considering its surface area (available for stimulation). Other region providing vigorous cough response to mechanical stimuli is trachea, carina and large bronchi [4, 24, 31]. Touch-like stimuli that initiate mechanical cough provide small, very short, very fast, and frequent deformation of the airways surface. Cough receptors do not respond well to inflation and/or deflation, supposedly to the macroscopic stretching of the airways [1, 8]. For example, compression of the trachea is not efficient stimulus to induce cough as well as bronchospasm and slow changes in airway pressure [1, 2, 39] at least under regular conditions.

Stretch-activated membrane channels provide majority of sensors sensitivity to mechanical stimulation [28–30]. Mechanical deformation of the airway surface (the receptor itself or the adjacent cells) results in receptor membranes stretch and opening of the ion channels. This allows positively charged ions (mainly Na^+) influx into the cell. When depolarizing effect is large, high frequency action potentials are generated at the nerve fiber [28]. Acid sensitivity of the cough receptors depends mainly (but likely not exclusively) on the presence of acid-sensing ion channels (ASIC) in their membrane [8, 40]. Complexity of the response as well as the interplay of various sensors in the cough response documents, e.g., that citric acid activation of cough receptors is modulated by the Transient receptor potential vanilloid 1 (TRPV1) channel antagonists [2], although these afferent fibers do not express TRPV1 channels [12]. Cough receptors respond effectively only to rapid reduction in pH and adapt to the stimulus quickly [8, 9]. The Transient receptor potential cation channel subfamily V member 4 (TRPV4) channels induce activation of guinea pig nodose ganglion cells [41–43] and the discharge in A-δ fibers in response to hypo-osmotic solutions. The interaction with adenosine triphosphate (ATP) P2X3 receptors represents a key osmo-sensing pathway involved in airway sensory nerve reflexes [41].

Cough mechanosensors generally express rapid adaptation, which is consistent with their no response to permanent stimuli such as airway pressure, lung volume changes, etc. The axons carrying the information to the brainstem are small myelinated and low speed (around 5 m/s) vagal fibers [1, 5]. They differ in their morphology as well as the conduction velocity from other myelinated fibers in the vagus

nerve such as those from slowly and rapidly adapting receptors. These 2 types of sensors arise typically deeper in the airways and lungs, transmit signals much faster (around 15 m/s), do respond to sustain stimuli such as bronchoconstriction and also ATP and induce bronchoconstriction as well as changes in respiratory pattern instead of cough [1, 5, 10, 30, 40].

2.3 Cough C-Fibers

Cough-related C-fiber endings respond to a variety of molecules that includes chemical irritants and inflammatory mediators. The highest sensitivity to chemical stimuli, e.g., SO_2, is deeper in the airways compared to mechanical trigger of cough [4, 31]. The function of this type of cough is mostly in removing irritants from deeper airways and in preventing to breathe dangerous chemicals into the lungs [38]. Afferent C-fibers are slow conducting (less than 1 m/s) thin unmyelinated fibers [5]. Among various subtypes of C-fibers composing the vagus nerve [5, 17], those with peripheral endings in the large airways (bronchial C-fibers that trigger cough) differ from those innervating peripheral lung tissue (pulmonary C-fibers that do not trigger cough) pharmacologically and neurochemically as well as by responses they activate [5, 28]. The phenotypic distinction between different vagal C-fibers represents the fact that, the neurons with the cell bodies in the nodose ganglia are derived from the epibranchial placodes, whereas the neurons with the cell bodies in the jugular ganglia are derived from the neural crest [44, 45].

Capsaicin is a very effective cough stimulant. The molecule activates (and opens) TRPV1 ion channel at the C-fiber endings [2, 46, 47]. TRPV1 is a nonselective, Ca^{2+}-preferring cation channel responding besides capsaicin to heat, acid, vanilloids (arachidonic acid derivatives), and direct phosphorylation via protein kinase C. Thus, it can be indirectly activated by inflammatory mediators such as ATP, bradykinin, nerve growth factor, or prostaglandin E2 via activation of their respective receptors [46]. For example, prostaglandin E2 and bradykinin activate airway sensors via EP3 and B2 receptors, receptively; both mediate effects through TRPV1 and Transient receptor potential ankyrin 1 (TRPA1) channel [19, 48–50]. TRPA1 agonists evoke coughing in guinea pig and human [14, 51]. TRPA1, which opens efficiently by ozone, allyl isothiocyanate, etc., is generally sensitive to stimuli that increase intracellular calcium. In addition, TRPA1 represents primary oxidant sensor [52] and is indirectly activated via TRPV1. However, TRPA1 activation seems less effective in inducing cough than TRPV1 activation [11]. Acid effectively stimulates bronchopulmonary C-fibers [8, 53, 54] via TRPV1, likely ASIC and also other ion channels and their functional interactions [9, 55]. Citric acid stimulates TRPV1 receptor-dependent (capsaicin-sensitive), tachykinin-containing C-fiber endings, but also capsaicin-sensitive and capsaicin-insensitive vagal afferents by a TRPV1-independent mechanism [47].

Nicotine and cigarette smoke produce action potentials in a subset of airway C-fibers, initiate cough [17, 56, 57], and cause urge to cough [58]. Nicotine activates ion channels nicotinic acetylcholine receptors at airway sensory nerve terminals of

C-fibers [59, 60], at least those with the cell bodies in the nodose ganglion [61]. Bradykinin causes coughing in human by activating B2 receptors localized on neurons in human nodose ganglia [16, 62] and jugular guinea pig afferents [63]. Bradykinin induces discharge in airway C-fibers [64–66] employing an action of TRPV1 and TRPA1 channels [19], similar to indirect activation of sensory endings by prostaglandin E2 via EP3 receptors [19, 67]. Also, prostaglandin D2 induces cough via DP1 receptor. This receptor mediates sensory nerve activation in mouse, guinea pig, and human vagal afferents [68]. ATP evokes discharge in nodose, but not jugular C-fibers [7] activating P2X receptors [69]. ATP induces cough in human [70], however, is inefficient, similar to adenosine and serotonin, in inducing cough in guinea pigs [6], which is likely related to the presence of 5-HT3 and P2X receptors [59] mainly in guinea pig nodose afferents.

2.4 Modulation

Besides stimulation of primary afferent pathways triggering cough, there are several modulatory phenomena: (1) Modulation of cough afferent path excitability occurs at the level of sensors, fibers, and central terminals. This modulation is local via alteration of membrane properties and channels, or reflex through synaptic actions from elsewhere. (2) Other peripheral inputs, including those providing feedback, such as nasal stimulation, nociception, muscles and joints mechanosensory stimulations, lung volume feedback, signaling in non-cough-related airway sensory C-fibers, etc., affect central processing of cough and consequently cough response. (3) Modulation of cough central neuronal network by pharmacological agents and/or by synaptic inputs results in changes in cough response.

Several other membrane receptors except for those directly involved in initiation of cough can alter membrane potential at vagal sensory endings. Ionotropic receptors (membrane ion channels) that can depolarize airway sensory nerve terminals include serotonin 5-HT3 receptors and ATP P2X receptors, metabotropic are (working via G-protein) bradykinin B2 and adenosine A1 receptors. Metabotropic receptors alter membrane potential indirectly via interaction with ionotropic receptors (such as TRPV1) and/or various types of calcium-activated channels [59]. Thus, the majority of inflammatory mediators does not directly evoke action potentials on C-fibers (at least when delivered ex vivo). However, even these may modulate the response of afferent neurons to other mechanisms of cough activation. Capsaicin or bradykinin delivered in the trachea or bradykinin inhalation (and even microinjections of capsaicin or substance P into solitary tract nucleus) can lower voltage for electrically induced cough in the guinea pig trachea [10]. Inhaled bradykinin potentiates citric acid-induced cough [39]. Responses initiated by C-fiber activation with capsaicin, bradykinin, cigarette smoke, etc. in guinea pigs are mediated in large part by central release of tachykinins [12, 39, 71–74]. C-fiber activation may thus sensitize the cough reflex via central mechanisms, too. Neurokinin Nk1 receptor agonists depolarize [75] or hyperpolarize [76] the membrane of nodose ganglion neurons depending on the species. Substance P is associated with an increase in C-fiber

activity and is potent cough stimulator in guinea pigs [74, 77, 78]. However, its inhalation had limited effect on citric acid-evoked cough [39] that may relate to various cough-inducing pathways for capsaicin- and acid-mediated cough. Aerosols of substance P do not cause cough in normal subjects, whereas it does in patients with common colds [73]. There is a participation of Nk2 and Nk3, in addition to Nk1, receptors in cough at least evoked by citric acid [78–80].

Acetylcholine, histamine, serotonin, and dopamine modulate (potentiate) cough evoked by inhaled capsaicin in conscious guinea pigs via muscarinic acetylcholine, histamine H1 and H2, serotonin 5-HT1A, and dopamine D1 receptors, respectively [81, 82]. Activation of histamine H1 receptors [13, 65, 83, 84] increases sensitivity of airway afferent C-fibers when mechanical and chemical (capsaicin) stimuli are applied [81, 85]. Inhaled histamine also increases citric acid-induced cough; interestingly, not just H1 but also ATP P2X and P2Y receptors are significantly involved [86, 87]. Levodropropizine acting on H1 and α-adrenoreceptors has potent peripheral antitussive ability [88, 89]. Prostanoids such as prostaglandins, prostacyclin, and thromboxane mediate diverse effects in the airways including cough modulation [90]. Prostaglandins mostly increase the excitability of sensory nerves [84]. Anandamide aerosol also induced cough in conscious guinea pigs via vanilloid VR1 receptors [91]. Consistent with a cough potentiation by muscarinic acetylcholine receptors, long-acting muscarinic receptor antagonists attenuate cough induced by the stimulation of TRPV1 receptors, but likely also ASIC and mechanoreceptors (Table 2.1) [92–94].

Modulation, in particular the inhibition of cough, is achieved by the action of nonselective inhibitors of phosphodiesterase (theophylline, theobromine, methylxanthine) and some selective inhibitors of it—PDE 1, 3, 4, and 5 [95]. Cough improvement has been shown in healthy and ovalbumin-sensitized guinea pigs for citric acid-induced cough [95, 96] and in human for capsaicin-induced as well as for chronic cough with no adverse effects [96, 97]. Theobromine and theophylline inhibit capsaicin-induced sensory nerve depolarization of guinea pig and human vagus nerve [96, 98].

Furosemide and other loop diuretics reduce cough evoked by citric acid, low-chloride solutions, and angiotensin-converting enzyme inhibitors in guinea pigs and humans [99–102]. Furosemide-sensitive Na^+-K^+-$2Cl^-$ cotransporter is expressed by sensory endings of nodose and jugular ganglia neurons [100]. The cotransporter inhibition by furosemide as well as the effect of Cl^- channel inhibitors likely reduces cough by inhibiting the activation of laryngeal and tracheobronchial sensory nerves [100, 103].

TRPV1 channels are involved in the modulation of cough reflex by several mechanisms. The enhancement of TRPV1 function at ganglion level (cough induced by capsaicin) was observed after a few days of the exposure of guinea pigs to low concentration of SO_2 [104]. Ethanol increased TRPV1 agonist resiniferatoxin-induced cough in guinea pig [105] and vice versa, cigarette smoke elevated threshold for capsaicin cough with no effect on TRPA1-mediated cough in human [106]. Reactive oxygen species cause activation and hyper-excitability of nociceptive afferents innervating the airways with likely key contributions of TRPA1 and

Table 2.1 Simplified summary of cough enhancing and inhibiting mechanisms and/or afferent inputs at the "cough initiating" loci

Stimulus/action on	Cough
Punctate-sensitive mechanosensors	++
Acid-sensing ion channels	++
Capsaicin and TRPV1 agonists	++
TRPV1 antagonists	--
TRPA1 agonists	++
TRPV4 activation	++
Menthol and TRPA1 antagonists	–
Irritants, e.g., SO2, ammonia, ozone, and cigarette smoke	++
Long-lasting effect of cigarette smoke (? peripheral effect ?)	–
Nicotine, acetylcholine, and acetylcholine receptor agonists	++
Prostaglandin E2 and EP3 receptor agonists	++
Prostaglandin D2 and DP1 receptor agonists	++
Prostaglandin D2 and DP2 receptor agonists	–
Bradykinin and B2 receptor agonists	++
ATP and P2X (P2Y) receptor agonists	++
Adenosine and A1 receptor agonists	+
Serotonin and 5-HT3 (5-HT1A) receptor agonists	+
Substance P and neurokinin Nk1 (Nk2, Nk3) receptor agonists	+
Histamine and H1 and H2 receptor agonists	+
Protease-activated receptor PAR1, PAR2 activators	+
Dopamine and D1 receptor agonists	+
α2 and β2-adrenoceptor agonists	–
Cannabinoid CB2 receptor agonists	–
Anandamide and VR1 receptor activators	+
Phosphodiesterase inhibitors	–
Furosemide and other loop diuretics, Cl^- channels inhibitors	–
Low Cl^- environment	++
Opioids and opioid receptor agonists	–
Nociceptin and NOP1 (other opioid) receptor agonists	–
Anesthetics	--
Laryngeal denervation	0
Presence of stretch receptors activity	++
Volume feedback (discharge changes of stretch receptors)	–
Pulmonary non-cough-initiating C-fibers (other C-fibers)	–
Rapidly adapting receptors	0 ?
Tetrodotoxin, cold and reduced fiber conductivity	--
Voltage-gated Na channel blockers	–

Data are pooled from various human and animal studies and represent "dominant effect" as effects may differ mainly in terms of intensity depending on species and/or site of application. Modulation by these stimuli/agents may occur at "non-cough-inducing" sites and may involve central mechanism, too. ++ = highly efficient in inducing cough response or very significant cough potentiation, + = cough potentiation, – = cough inhibition, -- = highly significant cough inhibition or cough response block. TRPV1 = transient receptor potential vanilloid 1 channel, TRPA1 = transient receptor potential ankyrin 1 channel, TRPV4 = transient receptor potential cation channel subfamily V member 4, EP3 = prostaglandin receptor, DP1 and DP2 = prostaglandin D2 receptors, B2 = bradykinin receptor, P2X and P2Y = purinoreceptors, A1 = adenosine receptor, 5-HT3 and 5-HT1A = serotonin receptors, Nk1, Nk2, Nk3 = neurokinin receptors, H1 and H2 = histamine receptors, D1 = dopamine receptor, α2 and β2 = adrenoceptors, CB2 = cannabinoid receptor, VR1 = vanilloid receptor, NOP1 = nociceptin opioid peptide receptor

TRPV1 [107]. Ozone enhances citric acid-evoked cough in conscious guinea pigs and rabbits, however, with little contribution of TRPA1 in guinea pigs. Interestingly, the effect was inhibited by bronchodilator drugs β2 agonists or muscarinic receptor antagonists [108]. Stimulation of protease-activated receptor-2 potentiated citric acid- and resiniferatoxin-induced cough in guinea pig by TRPV1 mechanism [109].

Opioids are known for their central inhibitory action on cough. They act primarily at opioid receptors, however, likely not exclusively [110, 111]. For example, in the cat, naloxone, a nonspecific opioid receptor antagonist, did not completely eliminate codeine suppression of cough [112]. Nociceptin opioid peptide receptors are expressed by airway vagal sensory neurons [113]. Nociceptin inhibits cough in guinea pigs and cats, perhaps acting at peripheral NOP1 receptors in the airways; generally, opioid receptors at the periphery may contribute to antitussive potency of opioid drugs [114–120]. Also, some peripheral GABA(B) receptor activity contributes to cough reduction [121]. The activation of α2-adrenoceptors [89, 122], β2-adrenoceptors, and cannabinoid CB2 receptors can inhibit sensory nerves and prevent cough [50, 123, 124]. Unlike DP1, the activation of prostaglandin DP2 receptors inhibited sensory nerve firing to capsaicin in vitro and in vivo [68]. Increased potassium conductivity of membranes at related neurons reduces their excitability. Thus, the drugs opening, e.g., ATP-sensitive potassium ion channels inhibit cough (Table 2.1) [125–127].

Also cough-inducing stimuli may modulate (potentiate or depress) coughing evoked by other stimuli. In anesthetized guinea pigs, C-fiber activation does not evoke cough, but greatly sensitizes the cough reflex evoked by activating the cough receptors [37]. For example, perfusing the trachea with a low Cl^- content buffer potentiated the acid-induced cough reflex, which is desensitized by capsaicin, atropine, and neurokinin receptor antagonists [47]. However, C-fiber activation also inhibits coughing in anesthetized animals [1, 3, 32, 128, 129]. Jugular C-fibers initiate and/or sensitize the cough reflex, nodose intrapulmonary C-fibers actively inhibit cough upon the activation [130]. At variance with cats and dogs, tracheobronchial cough is not significantly reduced in anesthetized rabbits during pulmonary chemoreflex (induced by C-fibers stimulation) [131].

Many stimuli largely activating rapidly adapting receptors (thromboxane, leukotriene C4, histamine, neurokinins, methacholine, etc.) are mostly ineffective in the cough induction [1, 132]. Thus, the role of these afferents in the regulation of cough is rather limited and surely unclear [40].

2.5 Vagus Nerve Conductivity

As the occurrence of regular reflex coughing fully depends on the vagus nerve conductivity, all interventions reducing afferent signaling in related nerve fibers result in degraded cough. As such, regardless of the stimulus, coughing is always attenuated by the anesthesia [1, 23, 31]; moreover, all the stimuli inducing cough via C-fibers are much less effective (are ineffective) under general anesthetic conditions [1]. Even intensity and/or efficacy of stimulation significantly affects

cough response. In anesthetized cats, reduced mechanical stimuli, putatively ¼ of control intensity, resulted in about half of a cough number and intensity of cough efforts, compared to that under control (preliminary data). Reduced conductivity of cough-related afferent fibers markedly reduces coughing. For example, unilateral vagal cooling blocking conductivity of myelinated axons that is supposed to reduce cough afferent drive (and coughing) approximately half had much higher effect on mechanically induced cough in anesthetized cats [133]. Consistent with these findings is the elimination of coughing when afferent pathway is completely abolished—vagotomy (in guinea pig section of recurrent laryngeal nerves for cough from larynx and trachea) [1, 2, 31, 134] and potentiation of the response when both tracheobronchial and laryngeal sites are stimulated simultaneously [135]. Coughing in anesthetized guinea pigs is almost fully abolished by the administration of tetrodotoxin [2]. Voltage-gated sodium channels (NaV) subtypes 1.7, 1.8, and 1.9 are expressed in sensory neurons including vagal sensory neurons that innervate the airways and initiate cough [136]. The conduction of action potential along cough-related vagal fibers depends on the activity of NaV1.7 that is tetrodotoxin sensitive. Interestingly, the initiation of action potentials in nerve terminals of nodose Aδ-fibers is entirely dependent on NaV1.7, while in nerve terminals of jugular C-fibers largely relies on NaV1.8 [6, 137–139].

2.6 Reflex Modulation of Cough

Cough is the complex reflex behavior modified by interplay of various peripheral and central signaling pathways, which depend on actual conditions. The chest movement is larger and faster, volume and pressure changes are extended, the airflows are faster and more rapid, glottis closure is more pronounced during cough than during a number of other behaviors (with an exception of sneezing). Several secondary pathways are involved in modification of cough performance including the feedback controlling the cough motor drive during the cough execution (Table 2.2). Among stimuli applied in the airway mucosa where cough is not induced, mostly chemical (irritant) stimulation is effective in the modulation of cough. Sub-threshold mechanical stimulation either to the nasopharynx [146, 147] or nose (continuous stimulations) [140] or pharynx [148] had no effect on any analyzed cough characteristics (Table 2.2) in experiments on anesthetized cats. Cough responsiveness (the number of efforts/stimulation time) was increased with the addition of capsaicin [141] or air puff stimulation to the nose in cats and guinea pigs ([141], Table 2.2).

Laryngeal cough reflex is eliminated by the anesthesia or transection of the internal branch of superior laryngeal nerves [31, 160]. Reduced efficacy of the cough response to the threshold fog stimulus in laryngectomized patients has been observed [161]. However, coughing induced by several other stimuli is unaffected by laryngeal denervation in both humans and experimental animals [162–165]. Vice versa,

Table. 2.2 Reflex actions and afferent inputs modulating coughing at the "non-cough-initiating" sites

Stim/event	CN	latency	I efforts	E efforts
Nasal mechanical[1]	0	0	0	0
Nasal capsaicin[2]	+	n	n	n
Nasal histamine[3]	0	n	n	n
Nasal puff[2]	+	n	n	+
Menthol, agonists of TRPM8[4]	–	+	n	n
Nasopharyngeal puff[5]	0	n	0	0
Pharynx+larynx water[6]	0	n	0	0
Stimulation (acid) of esophagus[7]	+	n	n	(+)
Baroreceptive drive—BP increase[8]	–	n	0	--
Abdominal, thoracic surgery[9]	(–)	(+)	n	–
Laparotomy[10]	n	n	n	–
Midline laparotomy dog[11]	n	n	n	0
Trachea, chest vibration[12]	(–)	(+)	n	n
Skin cold receptors[13]	–	n	n	n
Paralysis	(--)	(++)	n	(--)

Experimental animals' data as well as results of human studies. CN = normalized number of coughs, latency = the duration from the beginning of stimulation to the first cough, I efforts = inspiratory motor drive (diaphragm and/or parasternal muscles EMG) and/or inspiratory amplitude of esophageal (airway) pressure or inspiratory airflow, E efforts = expiratory motor drive (abdominal EMG) and/or expiratory amplitudes of esophageal (airway) pressure or expiratory airflow, mechanical = continuous stimulus by thick fiber or rubber piece, puff = air puff stimulus, TRPM8 = transient receptor potential channel subfamily M member 8, BP = arterial blood pressure, + = significant increase, ++ = highly significant and/or significant and large increase, (++) = observation without quantification, – = significant decrease, -- = highly significant and/or significant and large decrease, (--) = observation without quantification, 0 = insignificant and/or no change, n = not measured or non-applicable. Chemoreception drive exerts inconsistent effects on cough (see the text)

[1]Simera et al. [140], [2]Plevkova et al. [141, 142], [3]Plevkova et al. [143], [4]Laude et al. [144], Buday et al. [145], [5]Poliacek et al. [146, 147], [6]Poliacek et al. [148], [7]Ing et al. [149], Benini et al. [150], [8]Poliacek et al. [151], [9]Byrd and Burns [152], Dilworth et al. [153], Colucci et al. [154], [10]Clay et al. [155], [11]Farkas et al. [156], [12]Kondo et al. [157], Kashiwazaki et al. [158], [13]Yoshihara et al. [159]

thoracic vagotomy (below recurrent laryngeal nerve) preserving laryngeal innervation, besides almost complete elimination of tracheal cough, suppressed coughing from the larynx [166]. Discharge of slowly adapting pulmonary stretch receptors might be essential for the execution of tracheobronchial cough. It also significantly enhances the laryngeal cough response [128, 167, 168]. Indeed, the effects of altered stretch receptor activity on cough are not unequivocal and not clear [169–172]. Modified but not eliminated changes in volume feedback (irregular cough volumes and/or airflow resistances) are consistent with its suppressive and compensatory action on cough in anesthetized cats [173, 174].

Among other stimuli, cervical trachea or chest wall vibration inhibits cough [128, 157, 170], at least increases the threshold for initiation of cough by the

inhalation of citric acid in healthy males [158]. Similarly, the threshold for capsaicin- and citric acid-induced cough increased for few days after upper abdominal surgery [153] and the cough effectiveness was impaired (peak airflow during coughing was reduced) [154]. Even abdominal laparotomy can negatively influence cough [155, 156]. Post thoracotomy patients generate less pressure during cough, too [152]. Besides aforementioned nodose C-fibers, capsaicin-sensitive (and possibly other) afferents from the heart and splanchnic bed may inhibit cough, as cutaneous cold receptors do [128, 159]. Sensory information from other skin sensors provides rather limited modulation of cough [128, 175, 176].

The cough response can be sensitized by the sensory inputs from the esophagus [9, 128, 177]. Gastroesophageal reflux disease and/or esophagitis generally decreases threshold for initiation of cough [149, 178, 179] with no relation to the severity of esophagitis symptoms [150].

Nasal irritation, e.g., by capsaicin, and an inflammation potentiate cough [32, 128, 141–143, 180]. However, although nasal challenges with the agonists of TRPA1 receptors induce nasal symptoms (and increase the urge to cough), there is little effect on cough response [145]. Moreover, TRPA1 nasal stimulation (by allyl-isothiocyanate) reduced citric acid-evoked cough in guinea pig [181]. Also, TRPM8 receptor agonists, e.g., menthol, administered to the nose significantly inhibit cough [144, 145, 182, 183]. Menthol not only activates TRPM8 channels but also inhibits TRPA1 channels [184]. There is a little expression of TRPM8 in nerves innervating the lower airways, but large extent of it in trigeminal nerves innervating the upper airways [32, 183]. In addition to trigeminal afferents, also olfactory nerve endings, the smell perception and the interplay of these afferents represent a potential modulator (inhibitor) of the cough response in humans [145, 183, 185]. Pleasant taste perception (sweet) improves cough too; at least there is an evidence for increased cough threshold for capsaicin challenge [186].

Chemoreception drive exerts variable modulation of the cough reflex [128]. Acute hypoxia augments the response in the cat; however, severe degree is needed to affect cough in anesthetized animals [187–189]. Consistently, cough is reduced by carotid body resection [190]. Rather deep hypercapnia and its long duration are required for significant cough inhibition [189, 191, 192]. In general, brief hypocapnia and hyperoxia (a hyperpnea condition) reduce neither cough appearance nor its intensity as documented by severe cough attacks (the number of vigorous coughs in succession) present in animals and humans, even though such response results in large temporary hyperventilation. On the other hand, cough is inhibited by prolonged hyperoxia [193, 194].

Baroreception drive depresses cough. In anesthetized cats, experimentally induced increases and decreases in blood pressure resulted in clear suppression vs. enhancement of coughing induced by mechanical stimulation, respectively. Changes of cough temporal features as well as similarities to breathing alterations suggest that the modulation is accomplished at the level of shared neuronal circuits of breathing/cough central pattern generator [151].

2.7 Interaction of Motor Responses

Experiments on animal models (mostly cats) showed significant differences in the modulation of cough when motor response additional to cough is or is not induced and executed, even though the same and/or similar sensors are stimulated. The majority of mechanical stimuli in the airways that result in no motor reflex behavior barely affect coughing (Table 2.2). However, co-expression of different, sometimes opposite, behaviors usually significantly modulates cough performance. Cough responsiveness was reduced when aspiration reflexes (powerful abrupt and rapid inspiratory efforts due to the mechanical stimulus of the nasopharyngeal mucosa) occurred just prior to cough or within the inter-cough intervals (quiescent part of cough expiratory phase—E2) [146]. These effects correspond to prolonged latency to the first and subsequent coughs (prolongation of the cough quiescent E2 phase duration). The quiescent portion of cough expiratory phase (E2 phase) also prolonged with the presence of swallow; however, with swallow there was no significant effect on number of coughs in cats (Table 2.3) [195].

During combined trials, swallow, sneeze, and cough (rhythmic behaviors) always occurred in an ordered sequence without significant overlapping of their motor activities [140, 195]. During sneeze/cough trials each behavior is either cough or sneeze [140] and coughs or sneezes group together (they do not alternate one by

Table 2.3 Behavioral modulation of the reflex cough response

Stim/event	CN	latency	I efforts	E efforts
Nasal mechanical sneeze[1]	0	n	0	++
AspR before cough[2]	–	++	0	0
AspR quiescent phase E2[2]	--	++	0	0
AspR inspiratory phase[3]	0	n	++	+
AspR expiratory phase E1[3]	0	n	0	0
ExpR quiescent phase E2[4]	0	0	++	++
ExpR inspiratory phase[4]	0	n	++	++
ExpR expiratory phase E1[4]	0	n	++	++
Oropharyngeal swallow[5]	0	+	(+)	++

The majority of data are from the experiments on cats. CN = normalized number of coughs, latency = the duration from the beginning of stimulation to the first cough, I efforts = inspiratory motor drive (diaphragm and/or parasternal muscles EMG) and/or inspiratory amplitude of esophageal (airway) pressure or inspiratory airflow, E efforts = expiratory motor drive (abdominal EMG) and/or expiratory amplitudes of esophageal (airway) pressure or expiratory airflow, AspR = aspiration reflex, E2 = quiescent expiratory cough phase from the end of cough-related abdominal EMG activity to the next cough (respiratory cycle), E1 = active cough expiratory phase from the maximum of inspiratory EMG activity till the end of cough-related abdominal EMG discharge, ExpR = expiration reflex, + = significant increase, (+) = significant, however low increase, ++ = highly significant and/or significant and large increase, – = significant decrease, -- = highly significant and/or significant and large decrease, 0 = insignificant and/or no change, n = not measured or non-applicable

[1]Simera et al. [140], [2]Poliacek et al. [146], [3]Poliacek et al. [147], [4]Poliacek et al. [148], [5]Pitts et al. [195]

one). Swallow occurs in the anesthetized cat typically during the quiescent E2 phase of cough (termed phase restriction) [196]. Presence of swallows induced by injection of water in the oropharynx enhances subsequent coughs (Table 2.3) [196]. Co-occurrence of cough and sneeze resulted in increased cough expiratory efforts (inspiratory as well as expiratory component of sneeze, too) with no phase duration changes (Table 2.3) [140].

Short and immediate nonrhythmic responses such as aspiration reflex and expiration reflex (abrupt short-lasting expiratory efforts induced in the larynx and/or the trachea) can occur during any phase of cough, including the active cough inspiration and expiration. Transient inhibitions of cough inspiratory or expiratory activity occur with no change of the temporal cough feature [147, 148]. However, aspiration reflex in the cough inspiration [147] and expiration reflex anywhere within coughing bout improved cough efforts (Table 2.3). Expiration reflexes practically always precede cough and never merge into it [31, 148, 197] providing the first stage of the airway protection and defense.

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Brainstem Structures Involved in the Generation of Reflex Cough

3

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3.1 Introductory Remarks

Cough is a very complex motor act that can be voluntary, behavioral, or simply reflex aimed at defending airway integrity. In awake mammals, especially in humans, the contribution of the higher brain structures is prominent, not only when coughing is voluntarily initiated for different purposes (vocal fold clearing, psychological behaviors, etc.) but also when triggered by nociceptive airway stimulation either under physiological or pathological conditions. As it is usual for nociceptive stimulation leading under certain circumstances to pain sensation (the highest level of body defense), airway stimulation causes in awake subjects specific sensations ("urge-to-cough") that may trigger irrepressible coughing. Thus, it is very difficult to differentiate between reflex cough and cough produced under cognitive and emotional influences. Actually, nociception (especially when associated with pain) displays various components, such as those sensory-discriminative, cognitive, emotional, and reflex [1–3]. Cough and associated sensations are obviously defensive responses to nociceptive stimulation; thus, it is not surprising that cough and pain share similar features at both peripheral and central levels. This notion has been recently incorporated into the current knowledge of physiology and pathophysiology of cough [4]. Here we deal in particular with the cough reflex as produced in decerebrate or anesthetized animals as well as in anesthetized humans. Cough-related afferents terminate in the nucleus tractus solitarii (NTS) and have extensive projections both to the brainstem to generate reflex actions and to the higher brain structures to produce cough associated with the other nociception-related components. Interestingly, like pain sensation, it seems that also the

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"urge-to-cough" and consequent coughing displays placebo/nocebo responses (see, e.g., [1, 3, 5, 6]). Cough-related afferents generate the cough reflex by involving both respiration-related and non-respiration-related brainstem areas in a fairly complex way, although the prominent role is played by the neural structures containing respiration-related neurons and constituting the brainstem respiratory network. The central action of neuromodulators or neurotransmitters at the level of the various brainstem structures could help to understand the neural circuitry underlying this reflex.

3.2 Central Terminations of Cough-Related Afferents

The central projections of airway vagal afferents terminate in the brainstem where they innervate second-order neurons that in turn project to other brainstem nuclei and contribute to both reflex and higher circuits encoding various involuntary and voluntary motor responses as well as perceivable sensations. Neuroanatomical and electrophysiological studies in both cats and rats have demonstrated that the main central termination sites of primary afferents of rapidly adapting stretch receptors (RARs) that mediate cough-related inputs are the medial subnucleus of the NTS and the caudal aspects of the NTS (cNTS), especially the lateral portion of the commissural subnucleus. RAR second-order neurons (RAR cells) are located in these NTS regions. On the other hand, also bronchopulmonary C-fiber afferents convey tussigenic inputs and have their central terminations mainly in the medial portion of the commissural subnucleus, although a certain degree of overlapping exists between termination sites of RARs and C-fiber afferents ([7–11]; see for review [12]). Interestingly, RAR cells are excited by ammonia inhalation (a well-known tussigenic stimulus) and display monosynaptic EPSP in response to vagal stimulation. Studies in the rabbit [13, 14] using excitatory amino acid (EAA) receptor antagonists implicate that cough-related afferents activated by the stimulation of the tracheobronchial tree terminate in the cNTS consistently with previous findings. The results of investigations in guinea pigs both by anatomical tracing studies and by microinjections of EAA receptor antagonists [15, 16] led to the suggestion that afferent fibers activated in response to the stimulation of "cough-receptors" located in the tracheal mucosa terminate mainly in slightly more rostral and lateral NTS sites (lateral to the commissural subnucleus and, perhaps, in the medial subnuclei). The difference with previous findings in the cat, rat, and rabbit was attributed chiefly to the different site of tussigenic stimulation (trachea vs. tracheobronchial tree).

A permissive role of slowly adapting stretch receptors (SARs) in the cough reflex (see also Chap. 1 in this book) has been shown in some animal models, but not in others [16–19]. The importance of volume-related feedback in the regulation of the cough reflex is controversial, although both RARs and SARs may provide a significant contribution [20–24]. It has been shown that lung inflation [25] inhibits RAR cells and that SARs are responsible for inhibitory inputs to RAR cells via NTS second-order neurons, the so-called P cells. Really, two types of SAR second-order neurons exist. The first is represented by P cells, which receive virtually only SAR

(or pulmonary stretch receptors) afferent input, discharge during lung inflation and become silent if lung inflation is prevented (no-inflation test). The second is represented by Iβ (or Rβ) cells, which receive both central inspiratory drive and SAR afferent input and reduce their inspiratory discharge, but do not become silent, during the no-inflation test. SAR afferents project to the NTS subnuclei from the level of the obex to almost 1.5 mm rostral to it (cat). SAR second-order neurons have been found in the ventrolateral NTS, but also in other NTS regions, such as medial, dorsolateral, intermediate, and interstitial subnuclei [10, 26–29]. P cells are GABAergic or may corelease GABA and glycine ([8, 30]; see also [31]). Second-order neurons in the cough afferent pathway have been shown to project to brainstem neural structures involved in breathing pattern formation (see below), such as pontine and medullary respiratory groups [7, 10, 12, 32–36].

A schematic representation of more prominent synaptic inputs to RAR cells, originating especially from airway afferent fibers, is reported in Fig. 3.1 (for Refs. related to this illustration see [4]). Interestingly, several afferent inputs to the NTS imply the release of substance P. These sensory fibers include baro- and chemoreceptor afferents conveyed by vagus and glossopharyngeal nerves, trigeminal

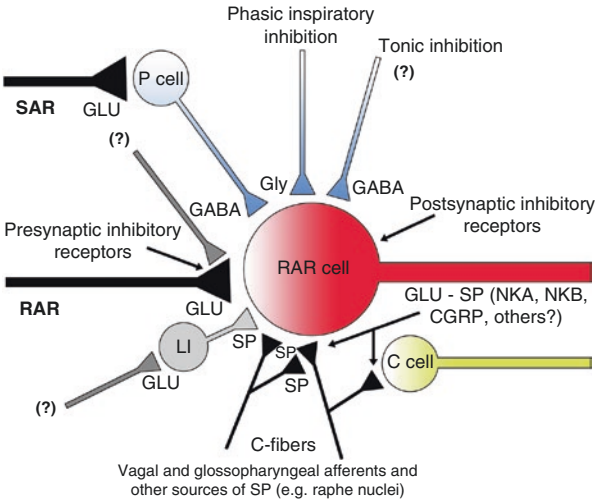

Fig. 3.1 Schematic representation of synaptic inputs to RAR relay neurons (RAR cells, red), a nonhomogenous NTS population of second-order neurons in the RAR afferent pathway which conveys also cough-related inputs. SAR, RAR, and bronchopulmonary C-fiber inputs modulate RAR cell activity through excitatory and inhibitory connections. P cells (largely localized in the medial and ventrolateral NTS regions, blue) are a subset of the entire population of second-order neurons in the SAR afferent pathway. C cells (yellow) are relay neurons of the bronchopulmonary C afferents located primarily in the medial portion of the commissural subnucleus. Convergence of C-fibers onto RAR relay neurons has also been reported. Abbreviations: *CGRP* calcitonin gene-related peptide; *GABA* γ-aminobutyric acid; *GLU* glutamate; *Gly* glycine; *LI* local interneuron; *NKA* neurokinin A; *NKB* neurokinin B; *RAR* rapidly adapting receptor; *SAR* slowly adapting receptor; *SP* substance P; (?) unknown sources that may include also vagal and glossopharyngeal afferents. (Modified from Mutolo [4])

afferents, skeletal muscle afferents, and projections from raphe nuclei (e.g., [37–41]; see also [42]). In addition, bronchopulmonary C-fibers have been suggested to converge onto RAR cells [43–45]. Indeed, the effects of substance P on NTS neurons are fairly complex since it displays not only postsynaptic excitatory effects but also presynaptic depressant effects on glutamatergic transmission between bronchopulmonary afferent fibers and second-order NTS neurons [12, 46, 47]. In addition, local interneurons may release substance P in response to glutamatergic inputs ([48], see also [47] for further Refs.). A comprehensive review on vagal afferent innervation of the airways and related central pathways under healthy or pathological conditions has recently been reported by Mazzone and Undem [49].

3.3 Brainstem Respiratory Network

Since cough is a modified respiratory act, it is appropriate to recall that the respiratory cycle is divided into three phases, i.e., inspiration, postinspiration or E1 phase, and expiration or E2 phase (active expiration) on the basis of the activity of the diaphragm and vocal fold adduction muscles (for details see Chap. 1 in this book). This triphasic organization is mirrored in the functional properties of the brainstem neural network underlying respiratory rhythm generation and pattern formation (see below).

Respiratory rhythm in adult mammals probably results from synaptic interactions between respiratory neurons located in the lower brainstem, particularly in the medulla oblongata (see e.g. [29, 50–54]). Several brainstem structures have been found to have a respiratory function. Respiratory neurons have been reported to be present in the rostral pons at the level of the parabrachial and Kölliker-Fuse nuclei, a region designated as the pontine respiratory group (PRG). Medullary respiratory neurons appear to be concentrated in two main aggregates, the dorsal respiratory group (DRG) and the ventral respiratory column (VRC). The DRG is closely associated with the NTS and contains mainly bulbospinal inspiratory premotoneurons. The VRC is located in the ventrolateral medulla and corresponds to a longitudinal column of neurons extending from the cervical spinal cord to the facial nucleus and comprises several rostro-caudally arranged compartments. The more rostrally located portion has been recently described and includes the retrotrapezoid nucleus (RTN) with the closely related parafacial respiratory group (pFRG), and the "Postinspiratory Complex" (PiCo).

Caudad there is a section of the column, initially named ventral respiratory group (VRG), which includes the Bötzinger complex (BötC), the pre-Bötzinger complex (preBötC), the inspiratory portion of the ventral respiratory group (iVRG), and the caudal expiratory component of the ventral respiratory group (cVRG). In the cervical spinal cord, two respiration-related regions have been described called the upper cervical inspiratory group (intermediolateral substance gray; [55]) and the high cervical respiratory group (close to the ventral surface; [56]). Both these two respiratory groups have not been reported to have any major role in the generation of respiratory activity and reflex cough.

The rostral VRG that comprises the BötC and the preBötC has a pivotal role in respiratory rhythm generation, while the iVRG and the cVRG are chiefly considered output systems. The iVRG compartment contains bulbospinal inspiratory neurons that project to spinal phrenic and intercostal inspiratory motoneurons. These neurons receive an excitatory input from preBötC excitatory neurons and an inhibitory input during expiration from BötC expiratory neurons. Both these inputs (along with other modulatory drives) shape and control the characteristic ramp-like pattern of inspiratory activity [57, 58]. Expiratory neurons are mainly concentrated in the cVRG and the BötC. Most of the cVRG expiratory neurons are bulbospinal neurons that project to spinal thoracic and lumbar expiratory motoneurons and receive their excitatory input from more rostral regions of the medulla ([29, 50, 59]; see also [52]). The BötC, which contains especially augmenting expiratory neurons, exerts extensive inhibition on medullary respiratory neurons. Convergent inputs from the BötC to the cVRG contribute to shape the pattern of discharge of expiratory cVRG neurons that drive expiratory motoneurons during eupneic breathing [29, 50]. The preBötC is located between the BötC and the iVRG and comprises several types of respiratory propriobulbar neurons. It has been proved to be the core circuit responsible for the generation of the inspiratory rhythm ([60]; for review see [52]).

Rostral to the BötC, the region located ventrolateral to the facial nucleus, i.e., the pFRG, contains pre-inspiratory neurons that usually discharge both prior to and after the phrenic nerve activity. This region was found to be activated in the respiratory cycle before any other respiration-related regions of the brainstem [61] and was first considered the source of both inspiratory and expiratory rhythmic activity. Successively, other studies proposed that this region is essential for expiratory rhythm generation in newborn, juvenile, and adult rats [62–66] since it contains many neurons silent under control conditions, but rhythmically active during the expiratory phase in response to pharmacological disinhibition or optogenetic excitation. When activated, the pFRG sends rhythmic excitatory drive inputs to cVRG expiratory neurons and, hence, to abdominal muscles (active expiration). However, at least in adult rodents, active expiration requires an ongoing rhythmic preBötC activity sufficient to drive inspiratory motor output [63, 66]. Expiratory muscle activation is also caused by neurons of this area under hypercapnic conditions [58, 64, 66, 67] or following peripheral chemoreceptor stimulation [68]. Moreover, the activation of serotoninergic or cholinergic muscarinic mechanisms within this region contributes to the appearance of neuronal expiratory activity and promotes the recruitment of expiratory motoneurons and active expiration [69, 70].

The pFRG partially overlaps with the adjacent chemosensitive RTN region located in a more ventromedial position (for review see [52, 71–74]). Since the pFRG and the RTN share some common features, they are often reported as RTN/pFRG. Neurons located within the RTN detect signals related to CO_2 and/or pH levels and transmit them to the preBötC and other brainstem sites. During the perinatal period its neurons also spontaneously generate late-expiratory bursts that raise preBötC excitability and may entrain preBötC rhythm activity. Then, the RTN loses its rhythmogenic role and functions only as a

chemosensitive center that detects environmental CO_2 and expresses a paired-like homeobox 2b gene (Phox2b). Interestingly, Phox2b mutations have been described in most human cases of congenital central hypoventilation syndrome ([75]; for review see [76]).

Recently, the brainstem region named PiCo, located rostral to the preBötC, dorsal to the BötC, and caudal to the facial nucleus, has been found to be characterized by rhythm-generating properties and has been considered necessary and sufficient for generating postinspiratory activity in both neonatal and adult mice [52, 77, see also 78]. On the basis of these results, a "triple oscillator model" has been proposed in which inspiration, postinspiration, and active expiration are generated by three distinct excitatory rhythmogenic microcircuits, i.e., preBötC, PiCo, and pFRG, respectively. The localization of the structures involved in the generation of the breathing pattern is illustrated in Fig. 3.2.

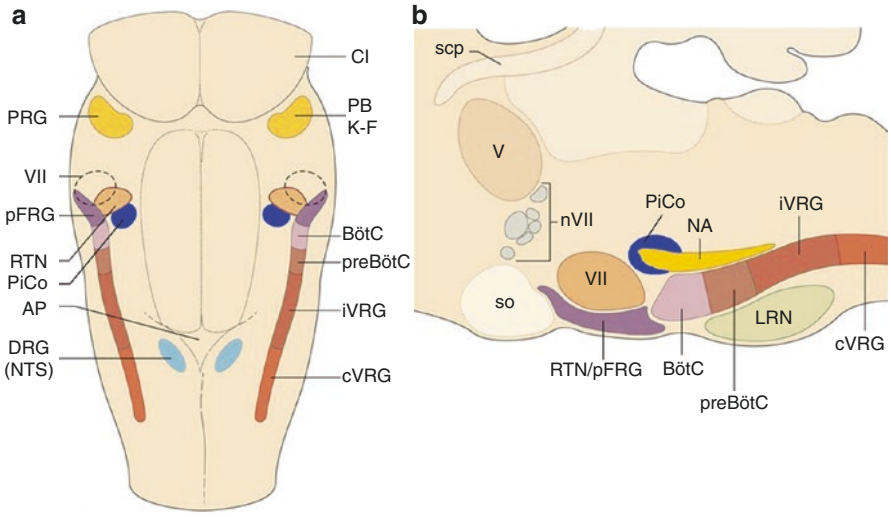

Fig. 3.2 Schematic illustration of the main brainstem neural structures involved in the breathing control. (**a**) Respiration-related regions have been projected on a dorsal view of the mammalian brainstem. *VII* facial motor nucleus; *AP* area postrema; *BötC* Bötzinger complex; *CI* mesencephalic colliculus inferior; *cVRG* caudal expiratory component of the ventral respiratory group; *DRG* dorsal respiratory group; *K-F* Kölliker-Fuse nucleus; *iVRG* intermediate or inspiratory portion of the ventral respiratory group; *NTS* nucleus tractus solitarii; *PB* parabrachial nucleus; *pFRG* parafacial respiratory group; *PiCo* Postinspiratory Complex; *preBötC* preBötzinger complex; *PRG* pontine respiratory group; *RTN* retrotrapezoid nucleus. (**b**) Parasagittal view of the brainstem containing the mammalian respiratory network. *V* trigeminal motor nucleus; *nVII* VII facial nerve and its nucleus; *BötC* Bötzinger complex; *cVRG* caudal expiratory component of the ventral respiratory group; *iVRG* intermediate or inspiratory portion of the ventral respiratory group; *LRN* lateral reticular nucleus; *NA* nucleus ambiguus; *pFRG* parafacial respiratory group; *PiCo* Postinspiratory Complex; *preBötC* preBötzinger complex; *RTN* retrotrapezoid nucleus; *scp* superior cerebellar peduncle; *SO* superior olive

3.4 Role of Brainstem Structures in the Generation of the Cough Reflex

Transection and lesion experiments in the cat have shown that the rostral pons and the cerebellum have modulatory effects on the motor pattern of the cough reflex, but the fundamental structures responsible for this reflex appear to reside in the medulla oblongata [79, 80]. For some previous reviews on the central neural mechanisms involved in the generation and/or regulation of the cough reflex, see, e.g., Fontana et al. [81], Pantaleo et al. [34], and Mutolo [4]. Former attempts to localize a medullary "cough center" within the NTS by using electrical microstimulation or lesion experiments have been reported (see, e.g., [34, 82]). However, these techniques do not allow to differentiate the role of neuronal structures and cough-related afferent fibers. In the light of the results of subsequent investigations on brainstem structures involved in the cough reflex, we can infer that the NTS is primarily the relay station of cough-related afferent inputs that are transmitted to the central neural network responsible for the generation of the cough motor pattern.

An interesting approach aimed at understanding the central mechanisms underlying the generation of the cough reflex has been that of investigating the behavior of medullary respiratory neurons during coughing in animal models, mainly cats. Earlier studies investigated the behavior of cVRG expiratory neurons in response to mechanical stimulation of the tracheobronchial tree or electrical stimulation of the superior laryngeal nerve [83, 84]. Expiratory neurons display excitatory responses during the expiratory phase of coughing. Furthermore, "latent" or almost quiescent neurons under normal breathing conditions can be recruited during coughing. Later studies reported that iVRG inspiratory and cVRG expiratory neurons are activated during the inspiratory and expiratory phases of coughing, respectively [85–87]. The same caudal expiratory neurons are activated during different types of expiratory efforts such as cough, sneeze, and expiration reflex.

All these studies mainly deal with the output system of the medullary respiratory network. More recent studies have investigated the behavior of different types of neurons located in more rostral rhythmogenic VRG regions during fictive coughing induced by superior laryngeal nerve stimulation in decerebrate, paralyzed, artificially ventilated cats. They have demonstrated that different types of inspiratory and expiratory neurons are activated during the appropriate phases of coughing [88]. Other studies carried out in similar preparations [89] revealed that a few inspiratory bulbospinal and propriobulbar neurons of the DRG are involved in cough response, thus suggesting that inspiratory premotoneurons responsible for the activity of phrenic motoneurons during the inspiratory phase of coughing are located elsewhere, possibly in the iVRG, in agreement with previous results [85–88]. Further studies have investigated the central mechanisms involved in the cough response evoked by mechanical stimulation of the tracheobronchial tree in anesthetized, spontaneously breathing cats focusing the attention on BötC expiratory neurons [90]. The majority of neurons encountered within this region display excitatory responses during the expulsive phase of coughing, in parallel with the main components of the abdominal electromyographic bursts and the corresponding increases in

tracheal pressure. The important role of the BötC neurons not only in providing the synaptic drive to cVRG expiratory neurons but also in determining the overall characteristics of the cough motor pattern has been corroborated by the suppression of both the inspiratory and expiratory components of the cough motor pattern observed during lignocaine blockades or following kainic acid lesions within this region in anesthetized, spontaneously breathing rabbits [91]. An important advance has been obtained by Shannon and collaborators that have extensively studied the behavior of rostral VRG respiratory neurons, including those located in the BötC and the pre-BötC, during fictive cough induced by mechanical stimulation of the intrathoracic trachea in decerebrate, paralyzed, artificially ventilated cats [36, 92–94]. Multi-site recordings employing microelectrode arrays and cross-correlational methods were used to functionally characterize respiratory neurons. They presented a model of the cough network and related synaptic interactions based on the behavior of respiratory neurons. The general conclusion of all these studies is that the rostral VRG neurons involved in the generation of the eupneic pattern of breathing also participate in the production of the cough motor pattern and that during coughing the drive to spinal motoneurons is transmitted via the same bulbospinal neurons that provide the descending drive during eupnea. These findings support the existence of multifunctional neural networks in the mammalian brainstem (e.g., [4, 34, 90] also for further Refs.) and, accordingly, of neurons that contribute to different functions, such as respiration, coughing, vomiting, and sneezing (see Fig. 3.3). When triggered by cough-related inputs to the NTS, the respiratory network appears to change configuration to generate the cough motor pattern. This hypothesis was advanced by Shannon et al. [94] who devised a neuronal respiratory network that undergoes a

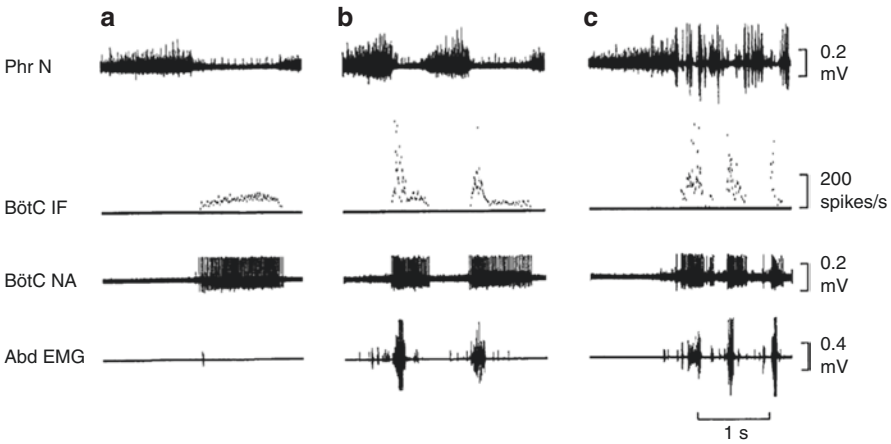

Fig. 3.3 Discharge pattern of one E-Aug neuron of the Bötzinger complex (BötC) displaying excitatory responses during coughing and sneezing induced by mechanical stimulation of the tracheobronchial tree and nasal mucosa, respectively. Pentobarbitone-anesthetized, spontaneously breathing cat. (**a**) Control discharge pattern. (**b**) Discharge pattern during coughing. (**c**) Discharge pattern during sneezing. *PhrN* phrenic neurogram; *BötC IF* instantaneous frequency of Bötzinger complex neuronal discharge; *BötC NA* Bötzinger complex neuronal activity; *Abd EMG* abdominal electromyogram. (Modified from Pantaleo et al. [34])

process of "reconfiguration" to produce coughing. A tentative computational model of coughing has more recently been described by Pitts et al. [95].

Interestingly, recordings from respiration-related neurons have been performed also in the RTN/pFRG region of guinea pigs during coughing and swallowing [96]. The majority of recorded neurons change activity in synchrony with coughing and swallowing. However, on the basis of brainstem transection experiments, it was concluded that RTN/pFRG neurons may modulate expiratory activity during eucapnic breathing, but are not essential components of the neural circuit underlying coughing and swallowing.

The results of recording experiments have been confirmed by studies on the expression of the immediate early gene c-fos during coughing [97, 98] and by lesion experiments ([91, 99–104] also for further Refs.). It has been shown that several brainstem regions either with or without respiration-related neuronal activities may contribute to generate or modulate the cough motor pattern. These regions include the BötC, the raphe nuclei and other midline structures, the periaqueductal gray, the lateral tegmental field, the PRG, and the reticular nuclei. The periaqueductal gray and the nucleus raphe magnus have also been reported to have suppressive influences on both coughing and swallowing ([105]; see also [106]).

3.5 Additional Neural Mechanisms Controlling or Modulating the Cough Reflex

Modulation or, in some instances, even generation of the cough reflex depend on the cerebellar nucleus interpositus [80], nasal mucosa trigeminal afferents [107, 108], esophageal vagal afferents [109], afferents from the external acoustic meatus (auricular branch of the vagus nerve, Arnold's or Alderman's nerve) that mediates the Arnold's ear-cough reflex (e.g., [110–112]), pharyngeal afferents (for review see [110]), chemoreceptors [18, 113–115] and baroreceptor [116] afferents. Of note, pharyngeal afferents from receptors probably traveling in vagal and glossopharyngeal nerves or in trigeminal branches can activate the gag reflex [117] and may also evoke coughing or the "urge-to-cough" [110].

Experiments performed in rodents (a species that lacks the cough reflex; see also [49]) have identified subcircuits in the brainstem and forebrain that receive relayed airway sensory inputs not only via the NTS but also via the paratrigeminal nucleus [118]. The NTS projects to several neural structures of the brainstem as well as to hypothalamic nuclei, well known components of autonomic and limbic/paralimbic central pathways. The central projections of the paratrigeminal nucleus are characterized by substantial input to the ventrobasal and submedius thalamus, which are important components subserving somatosensations, including those related to nociception. Interestingly, the paratrigeminal nucleus receives primary afferent projections from the pharynx, larynx, and tracheobronchial tree. In addition, visceral and somatic primary afferent inputs may converge in the paratrigeminal nucleus that has been suggested to be involved in the mediation of viscerovisceral and somatovisceral reflexes through efferent connections with autonomic centers in the brainstem. The paratrigeminal nucleus is certainly involved in some respiratory reflexes, but its possible role in cough production remains to be ascertained (see, e.g., [49, 119]).

Central and peripheral mechanisms involved in exercise and voluntary isocapnic hyperventilation may downregulate cough reflex responses [120, 121]. However, exercise (electrically induced hind limb muscular contractions) in ovalbumin-sensitized rabbits fails to produce similar effects [122]. An important characteristic of the cough reflex is its very strong dependency on the sleep-wakefulness state as well as on anesthesia ([123, 124]; see also Chap. 1 in this book). This reflex, in addition to a potent voluntary control, has also sensory, affective, and cognitive components. In fact, as revealed mainly by functional imaging studies, cough afferent pathways extend beyond a simple pontomedullary reflex to impinge on neuronal networks widely distributed throughout subcortical and cortical brain areas. The involvement of higher brain areas in the generation or modulation of coughing has been the subject of recent reviews (see e.g. [49, 125–128]). The main central and peripheral neural mechanisms that generate or modulate the cough reflex are schematically summarized in Fig. 3.4.

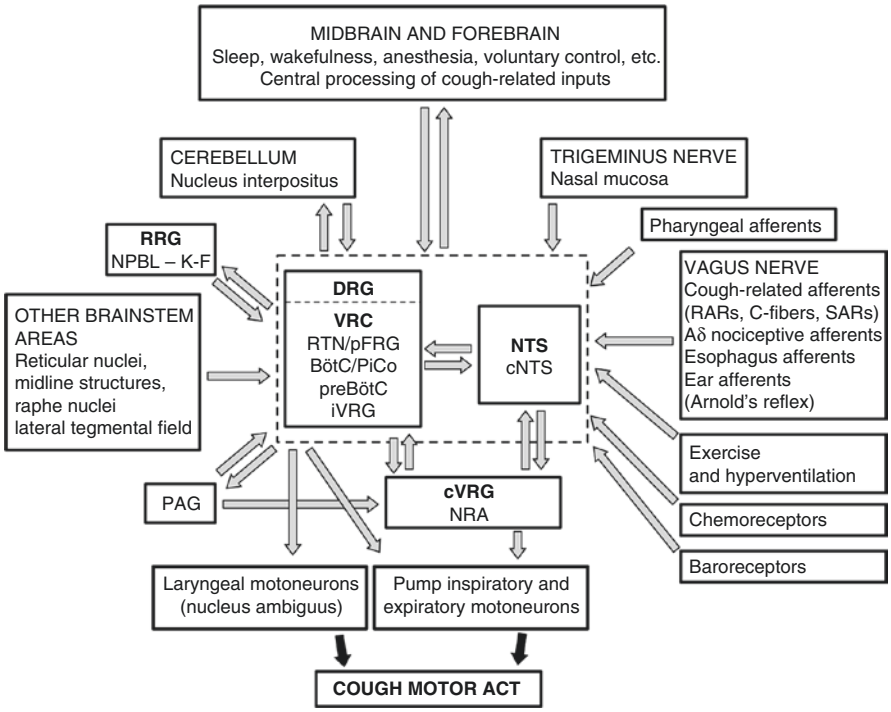

Fig. 3.4 Block diagram summarizing the main central and peripheral neural mechanisms involved in the production and modulation of the cough reflex. Possible connections between brainstem structures subserving this reflex have also been reported. Abbreviations: *BötC* Bötzinger complex; *cNTS* caudal aspect of the nucleus tractus solitarii; *cVRG* caudal ventral respiratory group; *DRG* dorsal respiratory group; *iVRG* inspiratory portion of the ventral respiratory group; *K-F* Kölliker-Fuse nucleus; *NPBL* nucleus parabrachialis lateralis; *NRA* nucleus retroambigualis; *NTS* nucleus tractus solitarii; *PAG* periaqueductal gray; *PiCo* Postinspiratory complex; *preBötC* preBötzinger complex; *PRG* pontine respiratory group; *RARs* rapidly adapting receptors; *SARs* slowly adapting receptors; *RTN/pFRG* retrotrapezoid nucleus/parafacial respiratory group; *VRC* ventral respiratory column. (Derived from Mutolo [4])

3.6 Insights into the Brainstem Mechanisms by the Action of Antitussive or Protussive Drugs

Centrally acting antitussive drugs have already been extensively reviewed (e.g., [4, 129–134]). Although the possibility exists that, following systemic administration, centrally acting antitussive drugs have sites of action at suprapontine and/or spinal levels, different lines of evidence have led to the general assumption that they act in the brainstem to suppress the cough reflex (see, e.g., [130]). According to earlier suggestions [14, 135], at least two medullary structures proved to play a prominent role in cough production and in the mediation of the central action of cough-related drugs, i.e., the first relay medullary station of the reflex pathway and the medullary neuronal aggregate responsible for the expiratory drive component of the reflex. These two neural substrates are the cNTS and the cVRG, respectively (see Fig. 3.5). This latter region corresponds, to a great extent, to the nucleus retroambigualis (NRA). Intracerebroventricular or intravertebral artery administration of antitussive drugs have demonstrated the central activity of some drugs. However, the main drawback of these methods is that they lack anatomical specificity. For antitussive drugs that may act in the brainstem, the specific site of action and the receptors involved are important issues. Microinjection techniques may well localize the drug into a given brain region, although with some limits (see, e.g., [138–140]). The interpretation of studies performed with these techniques has some difficulties since the employed drugs may act pre- or postsynaptically as well as on multiple subpopulations of neurons within the injected area. Furthermore, with these methods it is somewhat difficult to relate the dose of a given drug microinjected to the actual concentration reached when the drug is systematically administered.

The following presentation is mainly focused on the cNTS and the cVRG and deals largely with results obtained by our research group making use of bilateral microinjections of neuroactive agents in pentobarbitone anesthetized, spontaneously breathing rabbits. The localization of injections sites is diagrammatically represented in Fig. 3.5. Cough was induced either by mechanical or chemical (citric acid inhalation) stimulation of the tracheobronchial tree. Investigations on the role of drugs and, particularly, neurotransmitters or neuromodulators within different cough-related brainstem regions may primarily provide insights into the basic neural mechanisms subserving the genesis of the cough motor pattern and, in addition, hints for further studies on antitussive or protussive agents and for novel therapeutic approaches.

3.6.1 Caudal Nucleus Tractus Solitarii

Codeine and dextromethorphan, microinjected in large amounts and volumes into the NTS and the nucleus reticularis parvocellularis (lateral tegmental field), have been shown (see e.g. [129, 130]) to cause suppressant effects on cough in cats and guinea pigs. Recently, it has been reported that microinjections of relatively small amounts of codeine into the rostral NTS and the lateral tegmental field, but not in

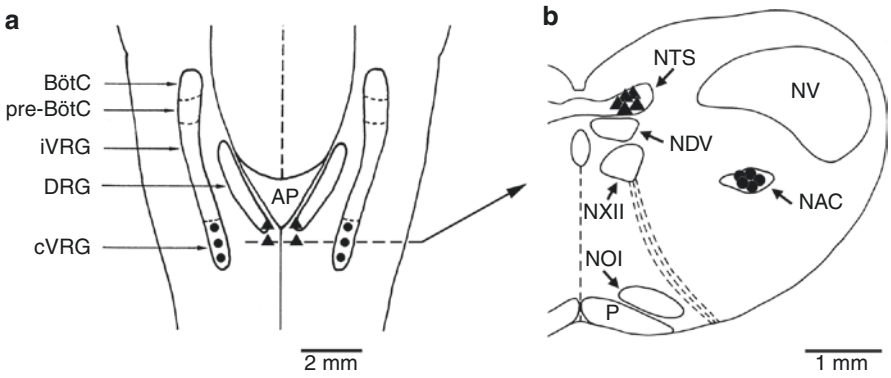

Fig. 3.5 Localization of injection sites. (**a**) A diagrammatic representation of a dorsal view of the medulla oblongata of the rabbit showing where bilateral microinjections of neuroactive agents have been performed into the cNTS (▲) and the cVRG (●), respectively. Abbreviations: *AP* area postrema; *BötC* Bötzinger complex; *cVRG* caudal ventral respiratory group; *DRG* dorsal respiratory group; *iVRG* inspiratory portion of the ventral respiratory group; *preBötC* preBötzinger complex. (**b**) Diagram of a coronal section of the medulla oblongata at the levels indicated in panel **a** (dashed lines) showing the location of representative sites where the microinjections have been performed. *NAC* nucleus ambiguous caudalis; *NDV* nucleus dorsalis nervi vagi; *NOI* nucleus olivaris inferior; *NTS* nucleus tractus solitarii; *NV* nucleus tractus spinalis nervi trigemini; *NXII* nucleus nervi hypoglossi; *P* tractus pyramidalis. (Outlines of some relevant structures derived from the atlas of Meessen and Olszewski [136] and the atlas of Shek et al. [137])

the cNTS, reduce cough in the cat [141]. In this connection, it seems appropriate to mention that codeine inhibits glutamatergic excitatory neurotransmission from primary cough-related afferents to second-order neurons of the NTS [142].

Blockade of non-*N*-methyl-D-aspartate (NMDA) receptors within the rabbit cNTS abolishes the cough reflex in response to mechanical or chemical stimulation, while only cough-depressant effects are induced by NMDA receptor blockade [13, 14]. An essential contribution of EAA receptors in the mediation of cough afferent inputs within the NTS has been observed in guinea pigs, but in regions more rostral and lateral to the cNTS and with a predominant role of NMDA receptors [16]. Recently, Poliacek et al. [143] have reported that in the cat bilateral microinjections of kynurenic acid, a broad spectrum EAA antagonist, into the cNTS are without effects, while similar microinjections into the rostral NTS cause marked alterations in both baseline respiratory activity and cough motor pattern. They have suggested the existence of important cough control mechanisms within the rostral NTS distinct from those processing the primary cough afferent signals located, according to the bulk of available literature, in caudal aspects of the NTS. Further investigations are needed to elucidate the involvement of different NTS subnuclei in the cough reflex. Interestingly, in accordance with previous findings by Mazzone et al. [45], the local application of substance P (NK1 receptor agonist) to the rabbit cNTS [14] potentiates or sensitizes cough responses by increasing both the amplitude of expiratory thrusts and the cough number, i.e., the number of coughs following each stimulation. The effects of C-fiber activation could be mimicked by microinjections

of capsaicin or substance P into the commissural NTS, and could be reversed by centrally administered NK receptor antagonists ([45]; see also [16]).

Local applications of the μ-opioid receptor agonist [D-Ala^2,N-Me-Phe^4,Gly^5-ol]-enkephalin (DAMGO) and the $GABA_B$ receptor agonist baclofen downregulate (decreases in the cough number and peak abdominal activity) or completely suppress the cough reflex [42]. Microinjections of the NK1 receptor antagonist CP-99,994 abolish cough responses while those of the NK2 receptor antagonist MEN 10376 are without effects [42]. These results are consistent with previous findings showing that tachykinin NK1 antagonists delivered to the brainstem circulation depress cough [144]. The antitussive action of baclofen microinjected into the NTS has been confirmed by Canning and Mori [16] in anesthetized guinea pigs. Furthermore, recently Kotmanova et al. [145] have reported that GABA, muscimol, and baclofen microinjected into the rostral NTS cause suppressant effects on the cough reflex, while at the cNTS level only GABA can suppress cough reflex responses. The reasons of the discrepancy with previous experiments are unknown and further comparative studies in different animal species are necessary to clarify the role of NTS subnuclei in the cough reflex.

Since cough can be considered a defensive response to nociceptive stimulation, it is not surprising that peripheral and central mechanisms underlying nociception and cough share similar features, including central stations in the afferent pathways and descending control mechanisms (e.g., [1–3, 49, 106, 131, 146–153]). Some important similarities between cough and pain have been reported in Table 3.1.

In humans, hypersensitivity in response to inhaled capsaicin has been found to coincide with elevated neural activity in the midbrain (nucleus cuneiformis and

Table 3.1 Some of the main similarities between cough and pain

Afferent fibers	
Aδ, C	Cough, pain
Receptors on sensory afferents	
$TRPV_1$,$TRPA_1$, ASICs	Cough, pain
ATP and adenosine receptors	Cough, pain
Bradykinin and prostaglandin receptors	Cough, pain
Histamine receptors	Cough, pain
Serotonin receptors	Cough, pain
Peripheral sensitization	Cough, pain
Central sensitization	Cough, pain
Corresponding clinical features	
Upper airway tickling sensation	Pain
Paresthesia	Cough
Hypertussia	Pain
Hyperalgesia	Cough
Allotussia	Pain
Allodynia	Cough

Derived from Mutolo [4]

periaqueductal gray). This enhanced activity in the midbrain is similar to that occurring in patients with chronic pain, thus supporting the notion that cough and pain share neurobiological similarities [106]. Of note, the periaqueductal gray is the source of one of the major descending pain controlling pathways (see, e.g., [149]). Since itch closely recalls the tickling sensation in the upper airways that leads to the "urge-to-cough" (e.g., [154, 155]), it seems relevant to recall that an interesting parallel has been made between pain and itch as well as between itch and cough [148, 156, 157]. Cough, pain, and itch obviously have important protective functions, but also characterize debilitating diseases under chronic pathological conditions ([147, 152, 153, 156, 157]; for further details and Refs. see [4]). Conceivably, neuroactive agents involved in the central control of reflex responses to nociceptive stimuli and associated pain sensation may also be relevant to the regulation of the cough reflex. Accordingly, attempts to downregulate the cough reflex have been made by using drugs suitable for pain control. Local applications of U0126, an inhibitor of ERK1/2 activation, have shown for the first time that the mitogen-activated protein kinase (MAPK) contributes to the processing of tussive inputs [150]. Bilateral microinjections of U0126 into the cNTS suppress cough responses without affecting the Breuer-Hering inflation reflex, the pulmonary chemoreflex, and the sneeze reflex. These results are coherent with those of previous studies showing that ERK1/2 has central effects on both acute pain behavior and neuronal plasticity underlying pain hypersensitivity (e.g., [158–161]). Similarly, the activation of α_2-adrenergic receptors by microinjections of clonidine and tizanidine, two agonists that may have analgesic effects (for review see [162–164]), has strong suppressant effects on cough reflex responses [165]. These α_2-adrenergic receptor agonists mainly act through the presynaptic inhibition of glutamate release, but also other mechanisms could be involved (see [165]). Another study [151] has been devoted to investigate the regulation of the cough reflex by galanin (a neuropeptide implicated in pain control) at the level of the NTS, where galanin receptors are known to be present [166]. Bilateral microinjections of galanin or galnon (a nonpeptide agonist at galanin receptors) into the cNTS markedly affect cough responses not only by decreasing the cough number and peak abdominal activity, but also by increasing the duration of the entire cycle of cough motor response. Galanin antitussive effects are possibly related to its interaction with substance P, opioids, and NMDA receptors [151]. Acetylcholine (ACh) applied to the cNTS has recently been shown to have depressant effects on the cough reflex mediated by muscarinic ACh receptors [167]. On the other hand, ACh is widely distributed in NTS and is a neurotransmitter profoundly involved in pain perception through both nicotinic and muscarinic receptors [168].

RAR cells located in the cNTS receive both phasic glycinergic and tonic $GABA_A$ receptor-mediated inhibitory inputs ([8, 25, 30, 169]; see also Fig. 3.1). Accordingly, evidence has been provided [31] that both $GABA_A$ and glycine receptors mediate a potent inhibitory control of the pattern of breathing and cough reflex responses. Bilateral microinjections of bicuculline and strychnine cause strong decreases in expiratory activity, marked increases in respiratory frequency, and potentiate the cough reflex mainly via increases in the cough number. Muscimol and glycine cause

opposite effects. Of note, an impairment of the activation of $GABA_A$ and glycine receptors can be the neural substrate of neuropathic pain ([170]; for review see [171, 172]). Taken together, these results strongly suggest that inhibition and disinhibition are prominent regulatory mechanisms of ongoing respiratory activity and cough reflex responses.

Noticeably, some drugs display a central protussive action. We have already mentioned that substance P potentiates the cough reflex by increasing expiratory drive and cough number. Consistently with the hypothesis of a central action of angiotensin-converting enzyme (ACE) inhibitors, that are known to cross the blood-brain barrier, microinjections of the ACE inhibitor lisinopril into the cNTS cause changes in the cough motor pattern characterized by increases in the cough number ([173] also for further Refs.). The complete blockade of lisinopril-induced cough potentiation was obtained either by bradykinin B_2 or NK1 receptor antagonism, thus suggesting a lisinopril-induced central accumulation of bradykinin and substance P. Accordingly, bradykinin microinjections into the cNTS induce a clear cough sensitization (increase in cough number), which is completely abolished by preceding microinjections of the NK1 receptor antagonist CP-99,994. In conclusion, the protussive effect of ACE inhibitors appears to be related to an action on NTS sensory neurons due to a bradykinin-induced release of substance P (see [173]).

Bolser and colleagues ([174, 175]; see also [15]) have proposed that in the brainstem is present a cough-gating mechanism. Their hypothesis is based on evidence derived from studies on the differential effects of antitussive drugs on the cough reflex and the breathing pattern. A cough-gating mechanism (probably constituted by a neural circuit including the population of second-order neurons in the cough-related pathways) may account for the fact that antitussive drugs generally do not alter breathing at doses that inhibit cough, thus implying that there exists a neural component important for cough that does not participate in breathing pattern generation. Furthermore, the finding that most antitussive drugs do not exert a generalized cough suppression, but specifically affect some components of the cough motor pattern, i.e., the cough number and the intensity of expiratory thrusts, is consistent with this hypothesis. The above reported results obtained in rabbits agree, to a large extent, with the assumptions of Bolser et al. [174, 175]. However, at variance with their hypothesis, some antitussive drugs have been found to change the timing component of cough probably affecting NTS neurons unrelated to vagal tussigenic inputs, but implicated in the control of respiratory timing and intensity [29, 50, 176] probably through ascending projections to neural circuits responsible for respiratory pattern formation (see [177] also for further Refs.). It seems possible that the cNTS is not a simple relay station, but plays more extensive functions in cough motor pattern generation and, in addition, that it may be an important location of the cough-gating neurons. At present, it cannot be excluded that different NTS subnuclei or other brainstem respiration-related regions may contribute to the cough-gating mechanism. On the other hand, species differences should be also taken into consideration (see [82, 95, 178], also for further Refs.). Examples of antitussive and protussive effects of some selected drugs have been reported in Fig. 3.6.

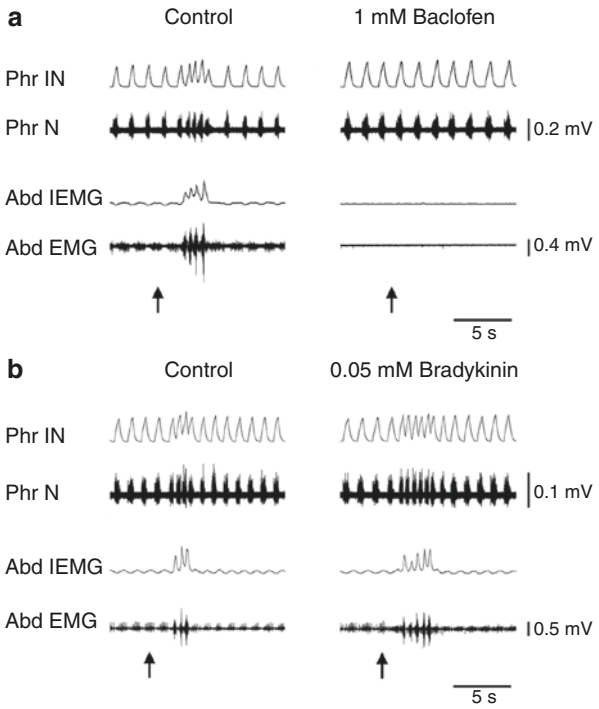

Fig. 3.6 Antitussive and protussive effects of selected drugs into the cNTS in anesthetized, spontaneously breathing rabbits. (**a**) Changes induced by bilateral microinjections (30 nl) of 1 mM baclofen into the cNTS. (**b**) Changes induced by bilateral microinjections (30 nl) of 0.05 mM bradykinin into the cNTS. Cough was induced by mechanical stimulation of the tracheobronchial tree (arrows). Traces are: *Phr IN* integrated phrenic neurogram; *Phr N* phrenic neurogram; *Abd IEMG* abdominal integrated electromyographic activity; *Abd EMG* abdominal electromyographic activity. (Modified from Mutolo et al. [42] and Cinelli et al. [173])

3.6.2 Caudal Ventral Respiratory Group (Nucleus Retroambigualis)

The cVRG is the region where bulbospinal expiratory neurons are located intermingled with other types of respiratory and non-respiratory neurons (e.g. [59, 179]) and, therefore, is strongly involved in the control of the cough reflex since the expulsive expiratory phase probably represents its most important component (see [177] also for further Refs.). Morphological and electrophysiological lines of evidence suggest that cVRG expiratory neurons probably are not involved in the respiratory rhythmogenesis since they seem to lack axon collaterals and therefore connections with other medullary respiratory neurons [29, 50, 59, 180, 181]. However, the activation of cVRG neurons causes transient inhibition of inspiratory activity in cats [182], rats [183, 184], and rabbits [135]. For instance, microinjections of the broad-spectrum EAA receptor agonist D,L-homocysteic acid (DLH) into the cVRG of the cat cause the activation of expiratory motoneurons and a corresponding silent period in phrenic nerve activity ([182]; see also [185]). Respiratory modulation triggered

by EAA receptor stimulation of the NRA region, comprising the cVRG, has been confirmed and analyzed in more detail by more recent studies [177, 186]. Available data support the possibility that caudal expiratory neurons can alter or shape the pattern of breathing via axon collaterals when strongly activated and that this could be relevant to some physiological conditions, such as airway defensive reflexes including coughing and sneezing [59, 182]. Anatomical studies showing cVRG projections to other brainstem respiration-related regions, such as the rostral VRG, the parabrachialis medialis/Kölliker-Fuse nuclei, and the NTS, are consistent with this view ([59, 177, 187–189]; for review see [4]).

The afferent drive inputs to the NRA are not completely unraveled. They may arise from more rostral expiration-related regions such as the BötC ([90, 93]; for review see also [34, 36, 59]) or the RTN/pFRG (e.g., [54, 61, 64, 66, 190–192]) as well as from the limbic system and the periaqueductal gray [177, 186].

Excitatory drive transmission to cVRG expiratory neurons appears to be mediated by glutamate with a major involvement of non-NMDA receptors. Bilateral microinjections of the non-NMDA receptor antagonist CNQX completely suppress spontaneous rhythmic and reflex abdominal activity [135]. More interestingly, they also suppress both the inspiratory and expiratory components of the cough reflex. This shows that neurons located in the cVRG are not merely elements of the expiratory output system, but are crucial for the production of all the components of the cough motor pattern. In fact, CNQX-induced effects on the inspiratory component of the cough reflex cannot be justified by the suppression of the excitatory output from cVRG bulbospinal neurons since Newsom Davis and Plum [193] have demonstrated that bilateral lesions of descending bulbospinal expiratory pathways deteriorate spontaneous rhythmic abdominal activity and block only the expiratory components of the cough reflex. It is worth noting that the existence of a cough-suppressant neuronal circuit within the cVRG has been shown by using DLH microinjections [185]. At variance with the suggestions arising from previous studies [90, 91], a cough-suppressant neuronal circuit has also been found within the BötC of the cat by means of similar microinjections [194]. The reasons for the discrepancy with previous findings are not clear and could, in part, be ascribed to differences in the preparation and microinjection procedures as well as to the nonhomogeneous composition of the BötC neuronal population.

Some antitussive drugs, already tested at the cNTS level, are active also within the cVRG mainly affecting cough number and expiratory thrusts. DAMGO and baclofen display inhibitory effects on the cough reflex [195]. Similar effects are also shown by the NK1 receptor antagonist CP-99,994, while the NK2 receptor antagonist MEN 10376 is ineffective. Furthermore, the cough reflex is reduced by tizanidine and completely suppressed by clonidine, thus supporting the notion of the essential role of this region in the production of the cough motor pattern [165].

Caudal expiratory neurons receive a potent bicuculline-sensitive GABAergic inhibitory input [196–198]. Accordingly, bilateral microinjections of bicuculline into the cVRG affect the ongoing pattern of breathing by increasing abdominal bursts and respiratory frequency, with a concomitant upregulation of the cough reflex. On the contrary, muscimol not only abolishes expiratory activity and decreases respiratory frequency, but also, like clonidine, induces the complete suppression of the cough

reflex [199]. These results show that $GABA_A$ receptors within the cVRG exert a very strong inhibitory control not only on the pattern of breathing, but also on airway defensive reflexes involving intense expiratory efforts. They further underline the role of inhibition and disinhibition phenomena in the central regulation of both breathing and coughing. Codeine and nicotine microinjected into the cVRG also cause depressant effects on cough responses in cats [200, 201].

3.7 Concluding Remarks

The central organization of the cough reflex is fairly complex and involves the brainstem respiratory network ("reconfiguration" hypothesis) and many modulatory influences that may contribute to the cough motor pattern formation. Several brainstem structures contribute to the regulation of this reflex, but at least two of them, i.e., the cNTS and the cVRG, are important sites of action of antitussive or protussive drugs. Interestingly, the results of drug microinjections suggest an essential role not only of the cNTS but also of the cVRG in the genesis of the overall cough motor pattern. Further investigations on the basic physiological and pathophysiological mechanisms underlying cough, pain, and itch, and the analysis of their similarities and differences, could suggest novel therapeutic strategies. Other studies are needed on the different brainstem areas subserving cough motor pattern formation and particularly on the RTN/pFRG that may be important in the generation of the expiratory thrusts, and on the PiCo that may have an essential role in the generation of postinspiratory behaviors which include coughing and swallowing. Moreover, the periaqueductal gray appears to be relevant to cough researches as indicated by some already mentioned lines of evidence (see [105, 106, 149]) and by the finding that it is the source of one of the major afferent input to the cVRG (e.g., [59, 177, 186]). Interestingly, also reciprocal connections between the periaqueductal gray and the preBötC have been reported [54, 202]. Although the preBötC is the core of the central mechanism generating the inspiratory rhythm, its contribution to the production of the cough motor pattern has not yet been completely unraveled. A recent aspect of the physiology of the central nervous system is the great contribution of glial cells, especially astrocytes, to the functional characteristics of neuronal activities (e.g., [203]). It has been proposed that astrocytes in the respiratory network may contribute to the characteristics of inspiratory activity [204–207] and play a crucial role in central chemoreception within the RTN [190, 208]. The finding that ozone-induced pulmonary inflammation results in a specific activation of vagal afferents that induces astroglial cellular alterations in the NTS ([209] also for further Refs.) suggests a possible involvement of astrocytes in cough regulation. However, the contribution of astrocytes to the modulation of the motor pattern of reflex cough remains to be investigated. Finally, it should be also remembered that many neuroimmune interactions can occur at different sites of the peripheral and central nervous systems in the development and maintenance of chronic cough, and that they could be interesting targets for studies aimed at developing novel effective antitussive therapies [210].

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The Cough Motor Pattern

4

Ivan Poliacek

Cough is defined as "a forced expulsive manoeuvre or manoeuvres, usually against a closed glottis and associated with a characteristic sound" [1, 2]. The definition is recommended for clinical studies with acoustic recording. The following definition is usually used in the basic science literature: "Cough is a three-phase expulsive motor act characterised by an inspiratory effort (inspiratory phase), followed by a forced expiratory effort against a closed glottis (compressive phase) and then by opening of the glottis and rapid expiratory airflow (expulsive phase)" [2, 3]. In our practice, when motor outputs (electroneurograms and/or electromyograms—EMG) and pressures are recorded, we employ the definition: Cough is characterized by a large burst of inspiratory-related parasternal and/or diaphragm EMG activity immediately followed by a burst of expiratory abdominal EMG activity and by a related negative to positive esophageal (pleural, intrapulmonary) pressure change [4, 5]. Cough employs fast expiratory airflow to clean the airways. Thus, the fundamental component of cough is the expiratory effort and related airflow. However, cough would be of limited efficiency without the preceding deep inspiration (Fig. 4.1; see also [6, 7]), the control of airway resistance (Fig. 4.2; see also [9]), the ability to generate force and produce ballistic-like expirations [3, 10–12], and appropriate timing–motor pattern resulting from activities of cough central pattern generator (Fig. 4.1; [13, 14]).

The inspiratory phase of cough results from an increased activation of inspiratory pump muscles, i.e., the diaphragm and external intercostals (Fig. 4.1; see also [3, 15, 16]). Their activity is driven by the motor pathway from cough central pattern generator via pre-motoneurons in the dorsal and ventral respiratory groups and spinal inspiratory motoneurons, including phrenic motoneurons [14, 17, 18]. There

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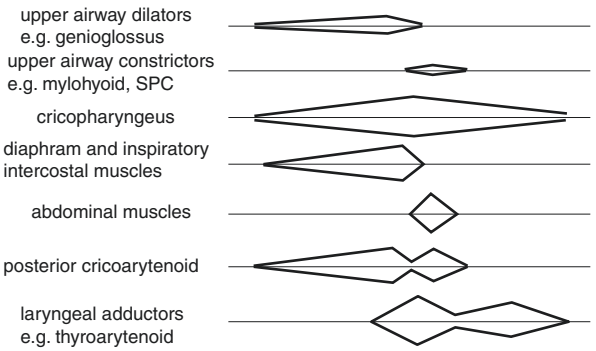

Fig. 4.1 Scheme of the cough motor pattern. The activations and inhibitions of the main pump and valve muscles are depicted. *SPC* superior pharyngeal constrictor. (Data are mostly in anesthetized cats)

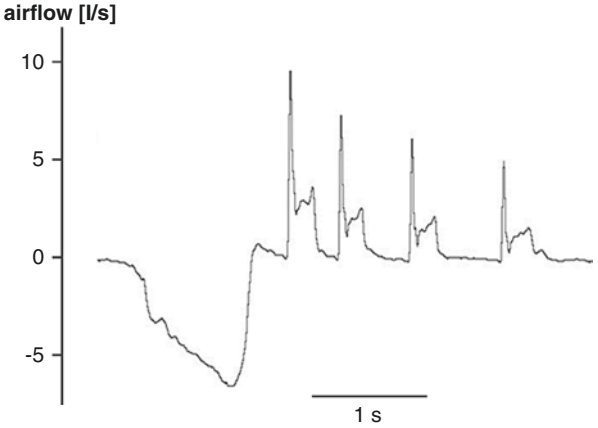

Fig. 4.2 Repetitive compressions and expulsions (re-accelerations) during coughing in healthy adults induced by capsaicin. Initial deep inspiration (negative airflow) followed by four compressive (practically 0 flow) and expulsive phases (abrupt increases in the airflow) with sequentially lower maximum airflow achieved in the next re-acceleration. (Modified from Hegland et al. [8])

are some differences in the electrical activity and/or contraction of various muscles in the inspiratory phase of cough [19, 20]; e.g., the activity of crural diaphragm and parasternal muscles is higher than that of costal diaphragm in cat [20] and mid-thoracic, synchronous with the diaphragm, external intercostal muscles discharge differently from caudal ones in decerebrate cats [19]. However, in general, the inspiratory pump muscles are activated during cough inspiration simultaneously and their peak activity reaches several times of that during quiet breathing [3, 20]. The diaphragm and external intercostal muscles electrical activity may persist or occur in the expiratory portion of coughs, probably contributing to eccentric control of expiratory movement [19–22].

The forceful expiration is produced by coordinated activity of abdominal muscles (Fig. 4.1; see also [3, 15, 16]). They work as a unit during coughing (unlike during loading) that has been fully confirmed in cats [23]. The motor pathway for expiratory motor output comes from the central pattern generator through

expiratory pre-motoneurons in the caudal ventral respiratory group and spinal motoneurons of iliohypogastric nerves [14, 24]. Caudal intercostal and mid-thoracic internal intercostal muscles discharge synchronously with the abdominal muscles in decerebrate, spontaneously breathing cats [19]. Triangularis sterni, involved in the control of the expiratory airflow in dogs, increases activity similarly to transversus abdominis [25].

In decerebrate and paralyzed preparations, nerve activities correspond well with activation of muscles executing cough [24, 26]. Thus, the fictive cough consists of large-amplitude burst of discharges in phrenic nerve immediately followed by a large burst in cranial iliohypogastric nerve [27].

Although, EMG activities of expiratory and accessory muscles during voluntary cough relate to cough flow and the basic cough pattern equals to that during reflex cough, EMG activities, burst durations and pressures—flows produced in reflex vs. voluntary cough may partially differ in healthy individuals [6, 22]. Voluntary coughs are usually stronger than reflex coughs (for various measures of cough intensity) and their lung volume initiation and lung volume excursion are greater [6, 28]. It surely reflects different origin of these coughs as well as the fact that maximum reflex cough would be achieved by intense suprathreshold and likely mechanical stimulus.

The principal regulator of airflow during cough is larynx [29]. Glottis widens during the inspiratory phase of cough due to the activation of laryngeal abductor posterior cricoarytenoid muscle (Fig. 4.1; see also [3, 30, 31]). Narrowing, up to complete closure of the glottis, is observed during cough inspiratory to expiratory transition—compressive phase (Figs. 4.1 and 4.2). Laryngeal adductors thyroarytenoid, lateral cricoarytenoid, and interarytenoid muscles are activated [29–32]. Reduction in the activity of adductors with the activation of laryngeal abductor (and cricothyroid muscle—the tensor in the dog, [31]) enhances the expulsive phase of cough (Fig. 4.1, [30, 32, 33]). Thus, the cough reflex includes three phases: preparatory inspiration, glottic narrowing—compression phase, and forced expiration [2, 3, 31]. The fourth phase of cough was also reported—the subsequent glottal narrowing, produced by another activation of laryngeal adductors [30, 32–35]. Subsequent constriction can represent laryngeal braking mechanism reducing the expiratory airflow after the cough expulsion and preventing of exhaling too much volume. Simpler monophasic patterns, at least for some laryngeal motoneurons, were found in decerebrate animals [36, 37].

Besides larynx, other upper airway muscles contribute to widening and stiffening of airway during inspiration (including that during quiet breathing) by activation of the alae nasi muscles, genioglossus, and pharyngeal dilators (Fig. 4.1, [9, 29, 38, 39]). Pectoralis major muscle expresses inspiratory activity in a deep breath, but inspiratory-expiratory discharges during cough in cats [40]. The superior pharyngeal constrictor is active in cough expiratory phase [41], the thyropharyngeus expiratory activity present in eupnea is reduced during coughing and cricopharyngeus discharges during all cough period with the peak in the inspiratory-expiratory transition in the cat (Fig. 4.1, augmenting pattern during inspiration and decrementing pattern during expiration; see also [42]). The styloglossus and levator veli palatini

muscles virtually silent in coughing are vigorously activated during the sneeze expulsion [41, 43].

Analogously to quiet breathing, pump muscle activities during cough (Fig. 4.1) result in pleural and intrathoracic pressure changes (Fig. 4.3) and corresponding inspiratory and expiratory airflows [3, 15]. Sharp increases in expiratory pressure and fast airflow changes result in rapid deformation of trachea and bronchi. A peristaltic wave is directed from bronchi upwards, likely improving clearing efficacy of coughing [3, 44]. The main expiratory flow usually begins as thoracic pressures rise; however, it can start at the peak pressure at least in voluntary coughing [45] that likely depends on glottal closure. Indeed, experimental as well as clinical data suggest that cough can be efficient and productive even without glottal closure and with low airflows [45]. For example, maximum cough pressures were similar to control

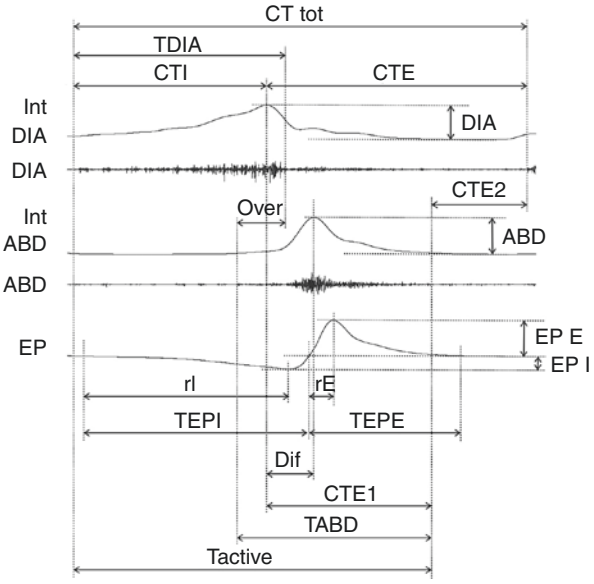

Fig. 4.3 The scheme of cough analysis. Amplitudes of EMG activities and esophageal pressure as well as temporal cough parameters are depicted. *ABD* abdominal EMG (also the amplitude of abdominal activity with the arrow); *CTE* expiratory phase duration; *CTE1* active portion of the cough expiratory phase; *CTE2* quiescent expiratory period; *CTI* inspiratory phase duration; *CTtot* total cough cycle duration; *DIA* diaphragm EMG (also the amplitude of diaphragm activity with the arrow); *Dif* interval between DIA and ABD activity maximum; *EP* esophageal pressure; *EP E* amplitude of expiratory EP; *EP I* amplitude of inspiratory EP; *Int* integrated moving average; *Over* overlap of DIA and ABD activity; *rE* duration of the expiratory EP rising part; *rI* duration of the inspiratory EP rising part; *TABD* duration of cough ABD activity; *Tactive* duration of all cough related EMG activity; *TDIA* DIA activity duration; *TEPE* duration of expiratory portion of EP; *TEPI* duration of inspiratory portion of EP. Unlike the pressure amplitudes, the time intervals for EP changes correspond well to the airflow alterations in the preparation with tracheostomy (anesthetized cat in this case). Ratios DIA/CTI, ABD/rising part of ABD activity, peak inspiratory flow/rI and peak expiratory flow/rE represent rates of increases for the particular measures (inspiratory activity, expiratory activity, inspiratory airflow, expiratory airflow), respectively

values after endotracheal intubation, even though the airflow began well before maximum pressure was reached [46]. The linear airflow velocity and mainly its acceleration essentially define cleaning efficacy of cough [8, 47, 48]. Lower peak flows but higher intrathoracic pressures (likely resulting in higher accelerations) may improve particle and mucus clearance and cough efficacy [49]. Voluntary coughs have maximum volume acceleration of about 300 L/s^2 [50]. Maximum derived velocities of expelled air during cough reach 5.0 m/s in women and 14 m/s in men [51]. Men are able to generate higher pressures and have shorter rise time to peak pressure/flow and glottal opening than women, too [52]. Consistent with the gender difference in the peak velocities is an unequal positive correlation between peak velocity time and cough peak flow rate in males vs. females [53]. Operating volume is the most important determinant of the peak flow achieved and volume expelled during coughing, but influences little the generated pressures [7]. The pressures correlate with effort-related EMG activities, the cough sound with both volumes and efforts [54]. In the cough peal, the pressures tend to maintain with increasing subsequent efforts [54]. Consistently, there is a poor correlation of the flow ratios and esophageal pressures in normal subjects [55], unlike for cough flows and related muscle integrated EMG variables [56]. Peak airflows and pressures correlate better with the height than weight of healthy subjects [52]. During coughing, a decrease in dynamic lung compliance, especially in the expiratory phase, was observed and the total lung resistance increased markedly demonstrating a concomitant bronchoconstriction [57, 58]. Moreover, the pattern of coughing can be to some extend voluntarily modified [59].

Cough is a rhythmic behavior. Coughing frequently occurs as an attack, peal or bout in the form of several repetitive coughs in succession. Coughs in sequence usually occur at largely predictable moment although they have unequal characteristics. In the cat, the strongest (and the shortest) response to the mechanical stimulus in the trachea is the eighth one, then coughs become weaker and longer again [60]. The pattern of coughing in humans typically represents several expulsions, each one preceded by the compression, following single deep preparatory inspiration (Fig. 4.2). These repetitive cough compressions-expulsions are termed re-accelerations [8, 59]. The duration of re-accelerations is shorter than single cough, less dependent on operating volume (their peak flow). During peals of coughs, repeated accelerations of flow resulted in more rapidly achieved required mechanical effect, suggesting improved efficiency of this pattern of coughing [7, 49]. Even endotracheal intubation, resulting in the flow not fully interrupted during the re-accelerations, does not impair the ability to develop normal cough pressures and the linear velocities required for normal airway cleaning [46]. However, due to the linear relationships between cough expired volume, flow rates, and the total number of coughs—re-accelerations, the mechanical effectiveness of later individual re-accelerations may decrease, particularly for the pattern of more than 3 re-accelerations [8, 46].

Re-accelerations resemble another defensive airway behavior, the expiration reflex [3, 61]. The expiration reflex represents rapid, short, and powerful expiratory effort without preceding inspiration. This reflex is primarily induced from the

glottis by mechanical stimulus. The expiration reflex is shorter, with extremely short latency; it rarely occurs in succession and it is regulated differently comparing with the cough response [3, 62–64]. For example, there is much lower sensitivity of this response to cough suppressants at least to those working at central sites [3, 62]. It is reasonable to believe that the expiration reflex is also generated differently than cough and very rarely intrudes among coughs, practically always precedes cough [62, 63].

Various parameters are measured during coughing. The threshold for initiation of the reflex expresses the lowest intensity of stimulus that results in the response, possibly the intensity evoking at least 2 or 5 cough responses (C2 and C5) within a determined time interval. Responsiveness represents the amount of response—number of coughs induced by a chosen constant stimulus. The pattern of individual cough reflex is determined by the activation of inspiratory and expiratory muscles executing cough inspiration and expulsion and also muscles regulating the airflow (mainly laryngeal abductors and adductors). Intensities, represented by amplitudes of electrical activation and/or mechanical effects of muscles, as well as temporal features, represented by the durations and sequencing of activities and/or pressures and airflows, describe complete pattern (Fig. 4.3; see also [2–4, 9, 12, 65–67]). It includes the situation of multiple expulsions that follow single preparatory inspiration—re-accelerations [8]. Additional characteristics inform about the rate of changes in the individual dynamic features, e.g., rate of rise for diaphragm or abdominal muscles activation, speed of increasing airflow, etc. (Fig. 4.3; see also [11, 12, 56, 65, 66]). The changes resulting from experimental or clinical interventions can be expressed using absolute or relative (percentages) measure related to control values [3, 4, 8, 16, 62, 68].

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Part II

Clinical Assessment of Cough

Acute and Chronic Cough

5

Giovanni A. Fontana

5.1 General Aspects

Coughing is one of the most common symptoms for which medical intervention is requested. In order to identify the cause(s) of the symptom and to establish a therapy that guarantees the highest probability of success, the doctor's intervention should first of all aim to define the character of acute or chronic cough.

The cough guideline developed by a specialist panel of the American College of Chest Physicians in 1998 suggested that cough be classified according to its duration [1]. Accordingly, the panel recommended cough be classified as acute (i.e. <3 weeks in duration), subacute (i.e. 3–8 weeks), and chronic (i.e. >8 weeks). Although this classification is reasonable, in the authors' experience is of little clinical utility and we prefer a more simple, duration-based classification of cough as acute (i.e. less than 4 weeks) or chronic (i.e. longer than 8 weeks).

5.2 Acute Cough

Numerous pathological conditions of very different severities can present coughing as the main symptom or accompanying other clinical manifestations [1, 2]. When evaluating patients with this symptom, it is important to direct the medical history and physical examination towards identifying the anatomical site of the pathological process responsible for the cough. The diagnostic approach in acute cough patients should also take into account the relative prevalence of conditions that may cause the symptom.

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5.2.1 Common Causes of Acute Cough

Among the most frequent causes of acute cough, in addition to the common cold, are acute bacterial sinusitis, exacerbations of chronic obstructive pulmonary disease, whooping cough, allergic rhinitis or inhalation of irritants. Less common causes are heart failure, pneumonia, pulmonary embolism and all clinical conditions characterised by aspiration of foreign material of oropharyngeal or gastric origin. In children, one of the uncommon causes of acute cough is the possible inhalation of foreign bodies.

The most common causes of acute cough have quite characteristic clinical presentations, and diagnosis can often be made by means of medical history assessment and physical signs, without resorting to instrumental diagnostic aids. Chest X-rays, blood gas tests and pulmonary function tests may be useful to confirm clinical suspicion of chronic obstructive pulmonary disease exacerbation. X-ray of the paranasal sinuses may reveal acute sinusitis.

5.2.2 Less Common Causes of Acute Cough

5.2.2.1 Heart Failure

In heart failure, coughing can occur together with orthopnoea as a premonitory symptom of possible acute pulmonary oedema.

5.2.2.2 Pneumonia

Pneumonia should also be suspected in the absence of fever, especially in elderly subjects, when coughing is associated with deterioration of general physical and mental conditions, dyspnoea and tachypnoea. A careful physical examination, supported by performing a chest X-ray, generally allows the disease to be diagnosed with considerable accuracy.

5.2.2.3 Pulmonary Embolism

Although it is frequently reported in the literature that coughing is a common symptom in patients with pulmonary embolism and that the disease should be suspected whenever coughing occurs in a patient with predisposition factors for venous thrombosis [1–3], an objective demonstration of the association between pulmonary embolism and coughing has never been clearly established. In contrast, a prospective study of a large patient population found coughing in 22 of 202 (11%) patients in whom angiography showed embolic obstructions of the pulmonary circulation, and in 45 of 298 (15%) patients with clinical suspicion of pulmonary embolism, subsequently excluded on the basis of negative pulmonary angiography or normal perfusion scintigraphy [4]. This study shows that coughing, rather than a symptom directly related to the presence of pulmonary embolism, can be more correctly considered as dependent on frequently coexisting cardiopulmonary pathological conditions in patients with clinical suspicion of pulmonary embolism [4]. In addition, it should be noted that the mechanisms responsible for any onset of coughing in

patients with embolic obstruction of the pulmonary vessels would be difficult to identify.

5.2.2.4 Aspiration Pneumonia

Coughing should be seriously considered in patients with clinical conditions characterised by alteration of the normal mechanism of swallowing at the oropharyngeal and oesophageal level, where inhalation of foreign material in the airways may cause aspiration pneumonia [5–7]. Aspiration pneumonia is a term that denotes lung damage, frequently observed in patients with anatomical or functional alterations of the organs involved in the swallowing process. The severity of the clinical picture depends on different factors such as volume, composition, acidity and possible bacterial superinfection of the aspirated material [5]. Many clinical conditions may predispose to aspiration; among these, the most common are chronic debilitating diseases, such as tumours or other diseases that interfere in a very marked way in the general state of the affected subject, psychiatric diseases, the treatment of psychiatric diseases with antidopaminergic neuroleptic drugs, Parkinson's disease, the motor alterations of swallowing caused by ischaemic brain lesions and all states of altered consciousness induced either by organic brain pathology, or anaesthetics, or abuse of drugs or alcohol. Aspiration pneumonia is one of the most frequent causes of adult respiratory distress syndrome (ARDS), and has a mortality rate of about 50% [8].

The diagnosis of aspiration pneumonia is essentially based on identifying a predisposing cause associated with a fairly typical clinical and radiological picture of lung involvement [9]. The clinical picture of patients with aspiration pneumonia is characterised by sudden onset of coughing, in subjects in whom the cough reflex is generally suppressed, dyspnoea, fever, widespread crackling in the thorax and marked hypoxaemia. The chest radiological findings are characterised by the appearance of multifocal lung infiltrates that tend to prefer the basal regions of the lungs. Often the radiological findings are bilateral, although the right lung is more often affected than the left one.

Only a small percentage of patients die in the acute aspiration phase. There is, in general, a rapid clinical improvement that is also manifested radiologically in a period of about a week. A subsequent deterioration of clinical condition is considered to be the expression of either a new episode of aspiration or bacterial superinfection. An association of the two unfavourable situations cannot be ruled out. Bacterial superinfection is generally due to contamination of the respiratory tract by oropharyngeal microbial flora. The bacteria most commonly involved, especially in conditions of poor oral hygiene, as often happens in patients hospitalised and suffering from chronic debilitating diseases, are *Pseudomonas aeruginosa*, *Staphylococcus aureus* and various species of Enterobacteria.

The therapy is essentially based on treatments to support severe clinical conditions in the acute phase and consists mainly of mechanical ventilation, the administration of oxygen at high concentrations in inhaled air and the infusion of liquids [9]. Antibiotics are useful only when they are targeted at pathogenic bacteria isolated from bronchial or oropharyngeal secretions. Corticosteroids do not prove

effective. In general, it can be said that measures to prevent aspiration in patients at risk, such as parenteral nutrition, are more effective than therapies undertaken after aspiration.

5.3 Chronic Cough and the Cough Hypersensitivity Syndrome

Chronic cough has long been defined as such on a merely temporal basis (see above) and sub-classified according with the most likely underlying cause of the symptom (ERS guidelines). Thus, in non-smoker patients with normal chest X-ray and not taking protussive drugs such as ACE-inhibitors, chronic cough is most commonly due to gastro-oesophageal reflux, asthma and non-asthmatic eosinophilic bronchitis, and rhinosinusitis, also termed upper airway cough syndrome. Although this approach to chronic cough proved to be clinically effective, it has soon been appreciated that a considerable percentage of patients are irresponsive to even maximal, symptom-driven treatment. These patients are diagnosed as suffering from an idiopathic form of cough, whereby the cough is not the clinical expression of an underlying disease but a disease in itself. Idiopathic chronic cough is also often defined as *unexplained chronic cough* (UCC) or *refractory chronic cough* (RCC) when respectively no precise cause can be found or when treatment of a potential cause fails [10]. Recently, a unifying paradigm has been proposed by which chronic cough represents a clinical entity where the cough is the major presenting problem, whatever the underlying condition. The condition is termed ***cough hypersensitivity syndrome***. Sensitisation of multiple peripheral and central neural pathways capable of eliciting cough account for the diverse clinical presentation of the various forms of chronic cough [11].

5.3.1 Common Causes of Chronic Cough

Given their high prevalence, posterior rhinorrhoea syndrome, asthma and asthma-like syndromes and gastro-oesophageal reflux will be covered separately in this the book.

5.3.2 Less Common Causes of Chronic Cough

Although some of the pathological conditions that will be covered below have a high prevalence in the general population, patients with these conditions rarely turn to a doctor for the cough symptom per se, as the focus is more on other symptoms or clinical manifestations.

5.3.2.1 Chronic Bronchitis

Coughing is one of the main symptoms of patients with chronic bronchitis. In fact, the disease can be diagnosed by a history of coughing and purulent expectoration

for most days in a period of at least 3 months for more than 3 consecutive years. Despite the high prevalence of the disease, only a modest percentage of patients who seek medical attention for chronic cough suffer from chronic bronchitis. In the prospective study by Irwin and his colleagues [12], only 5% of patients with a cough were attributed to chronic bronchitis, compared to much higher rates of coughing caused by posterior rhinorrhoea (41%), asthma (24%) and gastro-oesophageal reflux (21%). Although many smokers have chronic coughs, a study of the actual prevalence of this symptom is difficult to perform because smokers do not consider coughing as an expression of disease and do not resort to medical intervention (so-called "normal smoker's cough").

Coughing in patients with chronic bronchitis is mainly caused by the action on the airways of cigarette smoke or other inhaled irritating agents, such as dust or fumes in the environment. Cigarette smoke causes airway inflammation and hypersecretion of mucus, which can stimulate the afferent arm of the cough reflex. Patients with chronic bronchitis have a marked reduction in mucociliary *clearance* and, therefore, coughing plays a role as a necessary mechanism for airway hygiene. Coughing is, in fact, more frequent in the morning on waking up, when secretions have accumulated in the airways; it tends to appear more often during the day and also at night during exacerbation of the disease.

A diagnosis of chronic bronchitis is, as already mentioned, based on medical history findings. The disease can present clinically with different degrees of severity and, in the most severe cases, can be characterised by the presence of cyanosis, signs of peripheral oedema, respiratory failure with carbon dioxide retention and chronic pulmonary heart disease. Instrumental examinations such as chest X-rays, blood gas tests and functional respiratory tests are of considerable use in confirming the diagnosis of chronic bronchitis and assessing its severity.

The cough is resolved or reduced significantly in almost all patients who stop smoking cigarettes [12–14]. The drugs that can be used to treat chronic bronchitis (bronchodilators, inhaled steroids, anticholinergics and antibiotics), together with the attenuation of other symptoms characteristic of the disease, reduce coughing thanks to their beneficial effects on airway inflammation and glandular hypersecretion.

5.3.2.2 Bronchiectasis

In prospective studies on the causes of chronic cough, bronchiectasis was found to be responsible for the symptom in 4% of cases [12, 15]. Coughing in patients with bronchiectasis is probably due to accumulation of mucopurulent secretions in abnormal bronchial dilations secondary to both hyperproduction due to chronic infection and reduced clearance due to damage to the parietal ciliary system.

The most frequent causes of bronchiectasis alterations are, in childhood, recurrent infections, cystic fibrosis, aspiration of fluids or toxic gases, primary ciliary dyskinesia, and, in adults, chronic infections not properly treated, among which tuberculosis is very common. In recent decades, with the progress of anti-infective therapy, there has been a clear reduction in the prevalence of this clinical condition.

The symptomatology is essentially characterised by chronic cough with abundant sputum production (usually over 30 mL/day). A sputum-type vomiting that occurs in the morning on waking up to eliminate stagnant nocturnal secretions is typical. The excretion is usually very viscous and tends to increase in volume and take on a greenish colour during infectious exacerbations. Infectious pathogens are the most varied. Infection with various strains of *Pseudomonas aeruginosa* is typical for these patients. Other fairly frequent symptoms in patients with bronchiectasis are haemoptysis and the appearance of high fever during infectious exacerbations.

Diagnosis is based on clinical history, which is characterised by the chronicity of the symptoms. Chest X-rays can show lung regions with poor definition of normal bronchovascular anatomical structures, with bundling and dilation of the bronchi displayed longitudinally. The final diagnosis is based on performing a high-resolution computerised axial tomography, which can very clearly demonstrate alterations in the calibre and wall of the bronchi affected by the pathological process [16]. Bronchography, an examination considered in the past to be the diagnostic standard for bronchiectasis, has fallen completely into disuse following the advent of axial tomography, which also allows us to accurately study, in a non-invasive way, the extent and location of the pathological process for any indication of surgical removal.

The therapy is essentially medical and physiotherapeutic, with surgery limited to the infrequent cases of limited unilateral extension, in which the results of surgery are generally excellent [1]. The main focus of medical treatment is antibiotic therapy, which must necessarily be targeted at pathogens identified by cultural examination of sputum. It is necessary to avoid empirical therapies that may result in colonisation of secretions by bacterial strains with high resistance to antibiotics. Physiotherapeutic treatment is essentially aimed at facilitating the elimination of infected secretions from the airways and consists mainly of postural drainage, vibration and percussion of the chest walls and voluntary control of cough.

5.3.2.3 Post-infectious Cough

This term refers to a chronic cough that develops after an infection of the upper and/or lower airways in the presence of normal chest X-ray findings [1, 2]. This particular type of chronic cough often tends to be limited and resolve itself spontaneously. Inflammation of the airways following the primary infection is probably the aetiological agent of the cough. Diagnosis is based on identifying the previous infection in the medical history and ruling out other causes of chronic cough.

A typical post-infectious cough is that observed after whooping cough in children and adults. In adults, the diagnosis of whooping cough is based mainly on a history of previous contact with a known case of whooping cough. The cough tends to be spasmodic, more frequent at night and usually lasts for 4–6 weeks or longer. The initial characteristic inspiratory noise preceding coughing, commonly prevalent in children with whooping cough, is generally absent in adults. The diagnosis can be confirmed by identifying serum antibodies to *Bordetella pertussis* or by isolating that agent in nasopharyngeal secretions in the early (catarrhal) phase of the disease.

Since post-infectious cough generally resolves completely spontaneously, there is no fully reliable information on the outcome of specific therapies. Good results seem achievable with short-term therapy with inhaled corticosteroids or, if the cough is particularly bothersome, with oral corticosteroids [1]. If a diagnosis of whooping cough is suspected, treatment with macrolides or the combination of trimethoprim/sulfamethoxazole may be effective in attenuating symptoms and reducing the possibility of further transmission of the infection.

5.3.2.4 Bronchogenic Carcinoma

In the majority of patients with bronchogenic carcinoma, coughing can occur at various stages of the disease's course. In general, cough-free patients are those with neoplastic lesions involving the most peripheral bronchial branches, in which cough receptors are poorly represented [1, 2]. It is important to note that smokers, the category most at risk for the development of bronchogenic carcinoma, although frequently affected by coughing, mostly do not request health care for this symptom. This particular attitude (so-called "normal smoker's cough") can sometimes delay the diagnosis of bronchogenic carcinoma. A cough that develops for the first time in a long-time smoker, that presents variations in the usual characteristics or that becomes particularly insistent should be considered a possible indicator of the development of bronchogenic carcinoma, and should solicit further diagnostic investigations to confirm or exclude the clinical suspicion.

5.3.2.5 Coughs Due to Antihypertensive Angiotensin-Converting-Enzyme Inhibitor Drugs

All medications that inhibit the angiotensin I to angiotensin II converting-enzyme may cause coughing [17, 18]. In the prospective study by Irwin and his colleagues, taking these drugs was considered responsible for the cough in 2% of all patients evaluated [12]. Coughing may occur after more or less prolonged periods following the start of treatment. In some patients, the cough developed after taking the first dose, in others after weeks or months of therapy. The onset of coughing, which is characteristically non-productive and associated with a sensation of irritation of the pharynx, is not linked to the dosage of the drug. After stopping therapy, the cough resolves within 3–4 weeks [19]. Coughing during treatment with angiotensin-converting-enzyme inhibitors is probably due to the accumulation of inflammation mediators, such as bradykinin, substance P and prostaglandins, which are normally inactivated by the enzyme. The use of the drug losartan, a molecule that acts by antagonising angiotensin II receptors without inactivating the conversion enzyme, makes it possible to obtain antihypertensive pharmacological effects similar to those of angiotensin-converting-enzyme inhibitors, inducing coughing in a much more limited percentage of patients [20]. This observation is a demonstration, albeit indirect, of the pathogenetic relationship between converting-enzyme inhibition and coughing.

It is not possible to determine beforehand which of the subjects treated will develop the coughing side effect. The diagnosis is based on the clinical history of the appearance of the symptom after the beginning of therapy and its disappearance at the end of it.

5.3.2.6 Idiopathic Pulmonary Fibrosis

Coughing can be a very prominent symptom, along with dyspnoea, in patients with pulmonary fibrosis. The pathogenic mechanisms of coughing in this group of diseases are not known exactly. It is assumed that the cough is secondary to stimulation of the airway receptors, perhaps due to increased tension on them during the respiratory cycle due to reduced lung compliance.

5.3.2.7 Psychogenic or Habitual Cough

Psychogenic cough is a diagnosis that is reached when no other plausible cause is identified that could explain the symptom. This type of cough is most frequently described in children and adolescents [1, 2]. In adults with a chronic cough, the cause of the cough is usually identifiable without resorting to attributing the symptom to particular psychic conditions. Of the 153 cases of chronic psychogenic cough reported in the literature, 149 referred to patients under 18 years of age. No specific psychiatric disorder that could be directly linked has been identified. It is important to note that psychogenic cough is too often diagnosed in medical practice compared to its actual prevalence.

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Chronic Cough and Upper Airway Syndrome

6

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6.1 Definition and Pathogenesis

Posterior rhinorrhoea (PR) is a very common clinical condition that can be caused by a variety of diseases of the nasal and paranasal cavities. Among the nosological entities that most commonly underlie PR are common cold, seasonal allergic rhinitis, allergic and non-allergic perennial rhinitis, vasomotor rhinitis, postinfectious rhinitis, non-allergic rhinitis secondary to drug abuse or exposure to irritants, rhinitis during pregnancy and chronic sinusitis from various infectious agents. PR may also be caused by the irritative effect on the oropharynx and nasopharynx of cigarette smoke. Gastroesophageal reflux may cause the sensation of PR by means of the direct irritating effect of the gastric fluid flowing into the pharynx. In rare cases, PR can be caused by leakage of cerebrospinal fluid generally from traumatic lesions of the cribriform membrane [1, 2].

The pathogenetic mechanism of coughing during PR is likely to lie in stimulation of the afferent arm of the reflex in the upper airways by means of secretions descending from the nose and paranasal sinuses. Although the possibility of the cough reflex being initiated by aspirated secretions in the lower respiratory tract cannot be ruled out, there is no definite demonstration of this reflexogenic mechanism.

The clinical picture of coughing caused by PR is defined as posterior rhinorrhoea syndrome (PRS). This definition takes into account the fact that PR is a very common clinical condition that may or may not be associated with an equally

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common symptom, such as a cough, without there being a direct relationship between PR and the cough. Only when a causal link between PR and the cough can be established is it correct to use the definition of PRS. Many patients with typical symptoms for PR do not present with the cough symptom. It can be assumed that subjects with PRS differ from those with cough-free PR in the presence of chronic inflammatory changes that may make the afferent arm of the reflex more sensitive to the irritative stimulus of secretions descending from the nose and sinuses. PRS, secondary to a variety of rhinosinus conditions, is the most common cause of chronic cough. It remains unclear if the mechanisms of cough are the PRS itself or the direct irritation of upper airway receptors; in consequence, it has been proposed that the term upper airway cough syndrome (UACS) be preferred to posterior rhinorrhoea when discussing cough associated with upper airway conditions [3].

6.2 Prevalence

UACS is among the commonest cause of both acute and chronic cough in non-smoking subjects, with normal chest X-rays, and not undergoing treatment with converting-enzyme inhibitor drugs. Although there are no epidemiological studies defining the incidence of UACS during a common cold, it is evident that this condition, the most frequent among human conditions, is the most representative cause of transient acute cough. Proof that the common cold causes UACS is the significant concomitant reduction in PR and cough in patients treated with antihistamines and decongestants compared to untreated patients [4].

In large-scale studies in chronic cough patients, UACS has been shown to cause coughing in varying proportions, between 41 and 87% in the most recent studies [3, 5, 6]. This high prevalence of PR as a cause of coughing, higher than that of other common clinical conditions such as asthma and gastroesophageal reflux, highlights the importance of always taking into account the possibility of diseases of the nose and the paranasal cavities in evaluating patients with chronic cough.

6.3 Diagnosis

UACS may be suspected as a cause of chronic cough for which the patient turns to the doctor when symptoms are reported, such as a feeling of fluid going down into the nasopharynx and oropharynx, needing to clear the throat frequently, hoarseness, nasal congestion and anterior mucous or mucopurulent rhinorrhoea. Although patients may report these symptoms, they may only link them directly to the cough when specifically asked by the doctor. This behaviour of patients with UACS is comparable, albeit less so, to that of patients with gastroesophageal reflux who rarely connect the cough symptom with the functional alteration of the gastro-oesophageal junction. It highlights the importance of a very accurate history in subjects presenting chronic cough as their main symptom. Other relevant medical

history findings are a previous infection of the upper airway, sensation of intrathoracic hissing and, especially when UACS is caused by chronic sinusitis, sometimes abundant expectoration.

In taking the clinical history, it is important to detect the presence or absence of a family history of allergic conditions, whether the symptoms have a seasonal course and whether they are associated with particular environmental or occupational exposures or abuse of legal (topical nasal decongestants) or illegal (cocaine) pharmacological substances. This type of information is particularly relevant for the purpose of establishing the causes of rhinosinusitis and in guiding therapeutic intervention. Similarly, important in order to move towards an aetiological diagnosis is to determine whether the symptoms have appeared as a result of an upper airway infection and persist over time. This type of clinical presentation suggests the presence of sinusitis. The characteristics of secretions may be a further indication of the aetiology of PR. Clear, watery secretions are compatible with vasomotor or allergic rhinitis and, much more rarely, with losses of cerebrospinal fluid. Mucopurulent secretions are more likely to indicate the presence of sinusitis.

Inspection of the oropharynx and nasopharynx may reveal mucous or mucopurulent secretions and a characteristic appearance of the mucous membranes that presents widespread, small, round reliefs caused by submucosal lymphatic follicles made hypertrophic by chronic stimulation.

Most patients with chronic PR-induced cough have one or more of the history, symptoms and clinical signs described above; however, none of them, although highly sensitive, can be considered specific for UACS. The positive predictive value is limited because these symptoms and clinical signs are very common in the general population and may be present in conjunction with other conditions that cause chronic cough, such as asthma and gastroesophageal reflux. UACS can only be diagnosed with certainty when the clinical picture is resolved following specific therapy aimed at the rhinosinusitis considered to be the cause of the chronic cough.

The negative predictive value of the symptomatologic picture described above is close to 100% because in a very large study it has been shown that PR can be excluded as a cause of chronic cough in all patients in whom not one of the symptoms and clinical signs is detected [7]. In another study, however, it was found that in a small minority of patients without symptoms and signs related to upper airway involvement, the cough was resolved by antihistamine and decongestant therapy [6]. Although this finding can be interpreted as a demonstration of "silent" PR, it is likely that the suppression of the cough symptom may be linked to a possible nonspecific central sedative effect of the cough by antihistamines, especially if they are first generation.

None of the instrumental findings that can be obtained to better establish the rhinosinusitis pathological condition underlying the symptoms complained of by the patient can be considered pathognomonic in itself to diagnose UACS. Incorporating instrumental data with patient history, symptomatology and objective examination, however, allows UACS to be confirmed or ruled out with greater accuracy, especially in cases where an *ex juvantibus* therapy has not allowed the syndrome to be clearly defined.

The use of radiography of the paranasal sinuses in four projections (occipitofrontal, occipitomental, lateral and submental) is the standard method for evaluating of infections or tumours of the nasal and paranasal cavities. The radiographic findings characteristic of sinusitis are mucosal thickening greater than 5 mm and opacification of the sinuses [2]. Comparison with the results of bacteriology after rhinoscopy needle aspiration has shown that these radiological findings have a high positive predictive value in diagnosing paranasal sinus infection [2]. It has, however, been shown that mucosal thickening findings are poorly specific to establish a direct relationship between sinusitis and chronic cough [8]. In fact, in many patients with this radiological finding, the cough is resolved with therapies not specific for sinusitis (antihistamines and decongestants) and for this reason it is recommended that radiological examination be postponed to a drug trial [8].

As already noted, chronic cough caused by sinusitis is often associated with sputum production. In patients with chronic cough and sputum, X-ray of the paranasal sinuses has a positive predictive value of 81% in the diagnosis of UACS caused by sinusitis [9]. In patients with chronic cough without sputum, the positive predictive value drops to 57% [5].

A computerised axial tomography of the paranasal sinuses obtained on the coronal plane allows better definition of the anatomical structures compared to conventional radiography. There are currently no prospective studies comparing the accuracy of the two radiological examinations in diagnosing sinusitis. In general, it can be said that computerised axial tomography is to be used only in those cases which require an accurate assessment of any structural changes underlying chronic sinusitis or recurrent sinusitis.

A fibre-optic rhinoscopy exploration allows direct visualisation of the posterior two-thirds of the nasal fossae. It is indicated when persistent nasal obstruction is present. Sinusitis can be diagnosed using rhinoscopy, documenting the release of purulent secretions from the hosts of the paranasal sinuses [2, 7].

Other instrumental investigation techniques, such as ultrasound and magnetic resonance imaging of the paranasal sinuses, do not seem to provide particular advantages over those more commonly used.

In patients with a seasonal recurrence of symptoms or a history that indicates an association between symptoms and exposure to particular allergens, it is appropriate to perform an allergology evaluation, even if the positive test does not allow it to be proved with certainty that the cough associated with PR has an allergic aetiology.

In addition to the diagnostic information outlined in general in the previous paragraph, it is useful to highlight some distinctive clinical features of the various conditions that can cause PR and, consequently, UACS.

6.4 Allergic Rhinitis

Usually it has an onset in adolescence and is secondary to the activation of nasal mucosal mast cells by specific IgE. It can be divided into seasonal rhinitis, usually caused by pollens, and perennial rhinitis, more often attributable to mites, mould

and pet hair. Nasal symptoms are frequently associated with conjunctivitis and irritation of the palate and pharynx. Allergic rhinitis can be associated with other common manifestations of atopy, such as asthma and eczema. Skin allergy tests can be useful to identify the allergen(s) underlying the symptoms. A nasal swab allows eosinophilic infiltration to be detected.

6.5 Non-allergic Perennial Rhinitis

The presence of persistent symptoms is more characteristic of non-allergic rhinitis, which is generally of unknown pathogenesis. Diagnosis is based on the absence of family history of atopy and positive allergy tests. The characteristic symptoms of allergic diathesis, such as conjunctivitis, itching and irritation of the nose, palate and pharynx, are usually absent. This rhinitis group includes non-allergic eosinophilic rhinitis [10, 11], metachromatic basophilic rhinitis [12], atrophic rhinitis [12, 13], and immunological rhinitis, which may occur during various systemic immunological diseases, such as (Wegener's) granulomatosis, Churg-Strauss syndrome, relapsing polychondritis and Sjögren's syndrome [2].

Non-allergic perennial rhinitis may also include some clinical conditions caused by exposure to certain irritant chemicals, such as formaldehyde, nickel and chromium, or due to active or passive exposure to cigarette smoke. It is clear that medical history is the most important point in the diagnosis of these diseases.

6.6 Vasomotor Rhinitis

Clinically characterised by episodes of very abundant watery rhinorrhoea that occur suddenly and unexpectedly. It is assumed that this condition may be linked to an imbalance of the autonomic nervous system [12]. This pathogenetic hypothesis is supported by the good therapeutic results obtained through the use of anticholinergic drugs.

6.7 Drug-Induced Rhinitis

Prolonged topical use of vasoconstrictors or cocaine may cause subsequent marked vasodilation of the circulation of the nasal cavities as a rebound phenomenon [12]. Systemic drugs can also cause nasal complications. The most commonly involved pharmacological substances include beta-blockers, oral contraceptives, acetylsalicylic acid, disodium cromoglicate and ACE inhibitors [14]. The onset of symptoms with the beginning of therapy and the disappearance after therapy stops provide diagnostic evidence of this condition.

6.8 Rhinitis During Pregnancy

Apart from the most common rhinosinusitis inflammatory diseases that may occur during pregnancy, a specific condition of vasomotor rhinitis in pregnancy is described [15]. The symptoms are not specific and generally occur in the second or third trimester of pregnancy and, characteristically, they resolve within 5 days of delivery. From a pathogenetic point of view, it is assumed that this form of rhinitis may develop as a result of the increase in the volume of blood circulating and the concomitant vasodilating effect exerted by high blood levels of progesterone, which, together, would contribute to rhinosinusitis vasal congestion [15].

6.9 Postinfectious Rhinitis

This condition, which can also be defined as acute sinusitis, is characterised by a clinical history of previous infection of the upper airways, the symptoms of which do not resolve within a few days. The characteristic symptoms are purulent anterior and posterior rhinorrhoea with fever and paranasal pressure. Postinfectious rhinitis is resolved by medical treatment without leaving relics within 6–8 weeks [2]. The germs most commonly responsible for this form of rhinitis are *Haemophilus influenzae* and *Streptococcus pneumoniae* in adults and *Moraxella catarrhalis* in children [2].

6.10 Chronic Sinusitis

Chronic sinusitis is defined as the persistence of the characteristic symptoms of sinusitis for more than 8 weeks despite combined medical therapy. Symptoms are associated with radiographic evidence of mucosal thickening. In adults, chronic sinusitis can also be diagnosed in the presence of four or more annual episodes of acute sinusitis that persist for at least 10 days. In children, chronic sinusitis is defined as sinusitis lasting more than 3 weeks or as the presence of typical symptoms for at least five episodes in a year. In both adults and children, the presence of mucosal hyperplasia is necessary to diagnose sinusitis [16–18]. The symptoms are very variable and not specific and may include, in addition to the symptoms characteristic of acute sinusitis, also production of sputum, headaches and a persistent sense of nasal encumbrance.

The most common pathogens, both in adults and children, are anaerobic streptococci, alpha-haemolytic streptococci and staphylococcus aureus [16, 18, 19]. Most pathogenic microorganisms isolated in secretions are producers of beta-lactamases.

Among the conditions that cause PR, chronic sinusitis is the most frequent cause of chronic coughing, having been found in 39% of patients with UACS, followed by non-allergic perennial rhinitis (37%) and allergic rhinitis (23%) [5]. Other causes of UACS, such as postinfectious rhinitis, vasomotor rhinitis, drug-induced rhinitis or irritants, are responsible for very low percentages of UACS [5].

6.11 Therapy

The use of topical steroids and/or disodium cromoglicate is the basis for the treatment of all forms of allergic rhinitis, both seasonal and perennial. It is correct to combine local therapy with systemic therapy with second-generation antihistamines (with little sedative effect). Topical (oxymetazoline) or systemic (pseudoephedrine) decongestants can be used for short periods to relieve symptoms. The association of systemic decongestants with first-generation antihistamines (with a greater sedative effect) may be indicated in the presence of a lack of response to first-choice therapeutic approaches.

The control of environmental factors, in order to avoid contact with specific allergens, is perhaps the most effective intervention in allergic rhinitis. Desensitising immunotherapy should be considered when for two consecutive seasons intranasal steroids associated with disodium cromoglicate, antihistamines and possibly decongestants have not been able to control symptoms. Sometimes in the forms of allergic rhinitis with particularly severe symptoms, a cycle of a few days (usually 5 days) with systemic steroids may be necessary. In patients with particularly abundant and watery secretions, the use of anticholinergic drugs (ipratropium bromide) can be particularly useful in reducing rhinorrhoea [1, 2].

Topically acting steroids, antihistamines and decongestants are the basic therapy for non-allergic perennial rhinitis. Unlike allergic rhinitis, it is more appropriate to use first-generation antihistamines, which have a greater sedative side effect and a more pronounced anticholinergic action than more modern antihistamines [1, 2].

Environmental control, especially of occupational exposure, is a cornerstone of the treatment of non-allergic perennial rhinitis caused by irritants [17].

Topical treatment with ipratropium bromide can be very effective in vasomotor rhinitis [2, 20]. Surgical turbinate reduction can be considered in the event of failure of medical therapy.

Antibiotic therapy against the most commonly involved bacterial agents is the main focus of therapy for postinfectious rhinitis and sinusitis. In acute forms, the use of first-generation antihistamines and systemic decongestants may be particularly useful. In chronic forms, antibiotic therapy must be extended for at least 3 weeks to allow the infection to be eradicated. A lack of response to the therapy established indicates the need to perform cultural examinations on the aspirate from the sinus cavities. Topical steroids, antihistamines and decongestants can help to reduce the inflammatory reaction and relieve symptoms. In cases refractory to medical therapy, surgical intervention may be necessary to drain the infected cavities.

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Chronic Cough During Bronchial Asthma

7

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7.1 General Aspects

Bronchial asthma is a chronic inflammatory disease of the airways in which numerous cells such as mast cells, eosinophils, T lymphocytes, macrophages, neutrophils and epithelial cells are involved. Inflammation is associated with an increase in bronchial responsiveness to numerous stimuli and widespread but variable bronchial obstruction, which is often reversible spontaneously or after drug treatment. Clinically, bronchial asthma is characterised by the presence of wheezing, chest constriction, dyspnoea and coughing [1].

For a long time, the first of these symptoms was considered the *conditio* sine qua non for the clinical diagnosis of bronchial asthma. Studies [2–6] have, however, shown that coughing may be the predominant symptom of bronchial asthma.

According to current knowledge, three subgroups of asthmatic cough have been recognised: classic asthma, cough variant asthma (CVA) and eosinophilic bronchitis (EB).

The importance of establishing or refuting the diagnosis of asthmatic cough lies in the therapeutics as it may be considered as a treatable trait. The three subgroups can respond to anti-inflammatory asthma therapy [7].

Persistent coughing in asthmatic patients with good disease control may lead to clinical suspicion that the cough may be caused by concomitant conditions, such as gastroesophageal reflux disease or posterior rhinorrhoea syndrome, which are frequently found in association with bronchial asthma [8].

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7.2 Prevalence

Bronchial asthma is one of the most common causes of chronic cough, together with posterior rhinorrhoea syndrome and gastroesophageal reflux disease [8]. In studies with chronic cough patients, asthma was responsible for the symptom in percentages ranging from 10 to 40% [9–15]. It is important to note that this high prevalence of bronchial asthma as a cause of chronic cough cannot be considered representative for the general population, since all studies have been performed on select patient populations. At present, there are no epidemiological studies that have evaluated the prevalence of this form of asthma over the more classic clinical form. In an epidemiological study conducted on a population of more than 14,000 Canadian children [16], using standardised questionnaires, it was shown that, while 13% of patients reported history of persistent wheezing breath, only 6% of cases involved persistent coughing. These results, confirmed later by two other recent epidemiological studies [17, 18], support the possibility that coughing as an asthmatic equivalent represents a clinical variant of asthma that is less frequent than the more typical clinical forms of bronchial asthma.

7.3 Characteristics of Asthmatic Inflammation

As already mentioned, the pathophysiological characteristic of patients with bronchial asthma is represented by the presence of a chronic inflammatory state of the airways associated with hyperresponsiveness of the airways.

It is now established that the factors contributing to the onset of inflammation in asthma do not involve a single cell or a single mediator of inflammation, but are rather the result of complex interactions between inflammatory cells, mediators and airway epithelium cells [1, 19, 20]. The release of mediators from mast cells, macrophages, T lymphocytes and epithelial cells is the trigger for bronchial asthma. These mediators of cell origin induce the migration and activation of other inflammatory cells (eosinophils and neutrophils) in the airways, where they cause detachment of the cells of the bronchial epithelium, alteration of the control of airway tone by the autonomic nervous system, alterations in mucociliary function, hypersecretion of mucus and increased responsiveness of smooth muscle. Loss of airway epithelium integrity causes increased exposure of peripheral nerve endings located between the cells in the basal region of the epithelium. The activation of these sensory nerve endings determines, through an axonal reflex, the release of neuropeptides known as tachykinins (substance P, calcitonin gene-related peptide, neurokinin A and B) to bronchoconstrictor and tussigenic activity, which amplify the inflammatory process. The phenomenon of amplification of airway inflammation by neuropeptides is called “neurogenic inflammation” and is characterised by increased vascular permeability with plasma and oedema exudation, epithelial damage, hypersecretion of the submucous glands, increased bronchoconstriction and coughing. Inflammation of the airways causes an increase in bronchial responsiveness towards numerous stimuli in asthmatic subjects, as demonstrated by numerous observations.

First of all, inflammation markers, such as the number of eosinophils in sputum and bronchoalveolar lavage, the number of cells expressing messenger RNA for interleukin 5 and for macrophage growth factor (cytokines of primary importance in the recruitment and activation of eosinophils), correlate with levels of bronchial hyperresponsiveness [21, 22]. Secondly, with the treatment of asthma and the consequent reduction of inflammation markers, both asthmatic symptoms and hyperresponsiveness of the airways are reduced. Even if the presence of bronchial hyperresponsiveness in asthmatic patients is related to airway inflammation, however, the pathogenetic mechanisms responsible for bronchial hyperresponsiveness are quite complex and not only related to the presence of inflammatory cells in the airway.

Bronchial hyperresponsiveness is certainly related to the state of cell activation, to the release of mediators and cytokines and to the structural airway alterations caused by chronic inflammation [23]. The presence of a state of persistent bronchial hyperresponsiveness is an almost irreversible characteristic of the airways of asthmatic subjects and is probably related to anatomical alterations of the airways (remodelling of the airways). In addition, studies have shown that anti-inflammatory therapy reduces airway hyperresponsiveness but does not suppress it [24]. One of the main structural changes in the airways is the thickening of the reticular lamina of the basement membrane [19]. This histopathological alteration, sometimes already present in the early stages of the disease, has recently been confirmed in patients with coughing as an asthmatic equivalent [25]. Thickening of the basement membrane is caused by subepithelial deposition of collagen following inflammatory activation of myofibroblasts [25]. This alteration seems to remain unchanged even after prolonged treatment with corticosteroids [26]. Other histopathological features typical of airway remodelling found in asthmatic patients and also present in patients with equivalent asthma cough are subepithelial infiltration of eosinophils and macrophages, damage with denudation of the bronchial epithelium, oedema of the airway walls, goblet cell hyperplasia and thickening of the smooth bronchial musculature [19, 25].

7.4 Relationship Between Coughing and Bronchial Inflammation

Widdicombe [27] suggested that, in bronchial asthma, mediators released by airway inflammatory cells may activate both irritative receptors (RARs) and sensory endings of C-fibres. Activation of the irritative receptors, mainly located in the larynx and central airways, would be directly responsible for the onset of coughing, while activation of the sensory endings of C-fibres would cause, through the release of tachykinins, neurogenic inflammation and further stimulation of the irritative receptors. The effects resulting from stimulation of C-fibre endings by mediators of cell origin is, as specified elsewhere, yet to be defined. In fact, under some experimental conditions [27], the activation of these sensory endings even seems to have an inhibitory effect on the cough reflex. In summary, the genesis of coughing in bronchial

asthma depends on a complex interaction between inflammatory phenomena determined by the activation of C-fibres, activation of irritative receptors by mediators, and, finally, central inhibition of the cough reflex caused by stimulation of the sensory endings of C-fibres. The hypothesis that coughing in asthma is caused by the release of tachykinins from the nerve endings is supported by the following observations. In asthmatic patients, the use of tachykinin antagonists blocks coughing induced by inhalation of tachykinin-releasing agents (e.g. bradykinin); pharmacological inhibition of neutral endopeptidase, an enzyme linked to the membrane of many cellular elements of the respiratory tract that normally degrades tachykinins, leads to an enhancement of airway responses to substance P or neurokinin A [27].

Despite the fact that airway inflammation has the same histopathological characteristics in all clinical forms of asthma [19, 20, 25, 28], it is not clear why some asthmatic patients present coughing as the only clinical manifestation of the disease. McFadden [5] demonstrated that in asthmatic patients where cough was the predominant symptom of the disease, there was obstruction at the level of the large calibre airways; in patients where dyspnoea and wheezing breath were also present, the obstruction was predominantly localised at the level of the peripheral airways. Since it seems that the irritative receptors do not represent a homogeneous population but can mediate different responses in relation to their location in the tracheobronchial tree [29], it can be assumed that the involvement of localised irritative receptors at the level of the central airway more easily determines a cough, while that of more peripheral irritative receptors determines bronchoconstriction.

Respiratory function texts [2, 3] conducted in patients with coughing as an asthmatic equivalent, however, showed that, after bronchoconstriction induced by inhalation of methacholine or by physical exercise, the obstructive picture involved both the central and peripheral airways, similarly to what is found in the most typical forms of bronchial asthma. In addition, a study [28] in which the state of inflammation in both the central and peripheral airways was evaluated did not show significant differences in the characteristics and location of airway inflammation in patients with classic asthma compared to patients with cough as an asthmatic equivalent. It is likely that a thorough evaluation of the inflammatory state of the airways (e.g. with biopsies at the level of the carina and lobar bronchi), associated with the study of the functional role played by tissue mediators, such as tachykinins, may allow any differences in the characteristics of the inflammation accompanying the various clinical forms of asthma to be identified in the future.

7.5 Relationships Between Coughing and Bronchoconstriction

In 1964, Salem and Aviado [30] formulated the hypothesis that, in asthmatic patients, the contraction of the smooth musculature of the airways was responsible for the onset of coughing during crises of bronchospasm. In fact, the irritative receptors can be mechanically stimulated by the contraction of smooth muscles and inactivated by the action of bronchodilators [31]. In addition, it is documented that

tussigenic stimuli can also cause reflex bronchoconstriction [32]. The possible correlation between cough and bronchoconstriction may explain the frequent onset of coughing during methacholine- or histamine-induced bronchoconstriction, suggesting that coughing and bronchoconstriction involve a common afferent pathway. Other experimental data seem to indicate that the sensory mechanisms involved in the genesis of the two reflexes are distinct [33]. In healthy individuals, aerosols containing citric acid are able to cause coughing but do not induce bronchospasm, while in asthmatic patients the same agent determines the appearance of both types of response [33]. In asthmatics, inhalation of chloride ion-free isotonic aerosols induces coughing and only rarely bronchoconstriction, while inhalation of non-isotonic aerosols (and therefore also chloride-ion free) causes coughing and bronchospasm [34]. It is therefore believed that inhalation of chloride ion-free solutions selectively stimulates coughing; inhalation of hypotonic solutions, instead, leads to the appearance of bronchoconstriction [34]. In experimental animals, coughing induced by the administration of distilled water aerosols or non-isotonic saline solutions can be prevented by administering local anaesthetics into the airways, but this does not prevent the onset of bronchoconstriction [33]. On the contrary, the administration of sodium cromoglicate, which in asthmatic patients is able to prevent the onset of bronchoconstriction, prevents bronchospasm, but not coughing, in response to the inhalation of capsaicin [6].

7.6 Medical History and Objective Examination

In clinical practice, medical history allows bronchial asthma to be identified as a cause of chronic cough in a large percentage of patients.

The history should aim to obtain information about family history of allergic or pulmonary diseases, personal history of atopic diseases (milk crust, eczema, urticaria, rhinitis, food intolerances), the presence or absence of smoking habits, and work activity.

Coughs of asthmatic origin sometimes manifest themselves in a paroxysmal, accessional manner; they are triggered by both non-specific stimuli (exposure to fumes, irritating gases, cold air, hyperventilation induced by physical effort and laughter) and specific ones, such as exposure to allergens or substances for professional use [35–38]. Generally, the cough is non-productive, but sometimes it can be accompanied by the emission of small quantities of viscous secretions of a mother-of-pearl colour, resulting in the sensation of a considerable improvement in respiratory capacity [38]. During microscopic examination of sputum it is possible to observe numerous eosinophilic cells, Curschmann's spirals, made up of condensed mucus, Creola bodies, made up of agglomerates of epithelial cells, and Charcot-Leyden crystals made up of fragments of cell membrane and lysophospholipids of granules specific to eosinophils.

The objective examination may be completely negative in patients with a cough as an asthmatic equivalent or in those with classic mild to discontinuous asthma, when the subject is observed outside an asthma crisis. Only occasionally do deep

breaths or hyperventilation cause dry coughing. In patients who have a cough caused by moderate to persistent or severe asthma, chest auscultation shows the presence of continuous noises, generally of a high tone (hissing), mainly expiratory, which can be highlighted by having the patient perform a forced exhalation manoeuvre.

The asthmatic origin of a chronic cough can therefore only be diagnosed with certainty by demonstrating bronchial hyperreactivity and when the clinical picture is resolved following specific anti-asthmatic therapy [39].

7.7 Instrumental Findings

In most patients, blood chemistry tests and chest X-rays are normal; only in a minority of cases can eosinophilia and signs of pulmonary hyperinsufflation be found on chest X-rays.

The demonstration of asthmatic cough requires some evidence of variable airflow obstruction such as peak flow variability or reversibility to salbutamol of more than 12–15%. These investigations, in patients with normal lung function, have a very low negative predicted value [40]. Most patients with a cough as an asthmatic equivalent or with typical mild to discontinuous asthma in dormancy have normal respiratory function values, and administration of a short-acting bronchodilator drug does not result in significant changes in the basic functional parameters [35–38]. In these cases, the fundamental test for diagnosing a cough of asthmatic origin is the measurement of bronchial hyperreactivity [8, 35–39].

The diagnosis of bronchial asthma can therefore be reliably suspected when the patient has the fundamental characteristic of asthma, namely bronchial hyperreactivity.

Bronchial hyperreactivity is a marked response to a variety of non-specific (physical, chemical, pharmacological) or specific (allergens, drugs) bronchoconstrictor stimuli, which make the airways of asthmatic patients much more sensitive to reacting in a bronchoconstrictor sense than the airways of normal subjects [41]. Non-specific stimuli induce bronchoconstriction in most asthmatic patients regardless of the aetiology of the disease; some are more sensitive but less specific (such as cholinergic pharmacological stimuli), others are less sensitive but more specific (such as physical stimuli) and probably identify the category of patients with more severe disease. Specific stimuli induce bronchoconstriction only in subjects specifically sensitive to that compound, because they are sensitised by an IgE-mediated (as for inhaled allergens) or not IgE-mediated (as for occupational chemicals) allergic mechanism, or by a non-allergic mechanism (as for aspirin asthma or food additives).

In clinical practice, the test is conducted by having the patient inhale increasing concentrations (or doses) of a non-specific bronchoconstrictor agent (usually methacholine) through a nebuliser; inhalation is continued until the maximum deliverable concentration or until a reduction in FEV_1 equal to or greater than 20% of the baseline value. The results are expressed as provocative concentration (or dose) ($PC_{20}FEV_1$ or $PD_{20}FEV_1$) and expressed in mg/ml (or mcg) of methacholine; the

value is obtained from the dose response curve drawn showing on the abscissa the concentrations of methacholine and on the ordinate the percentage decreases of FEV_1 with respect to the base value. As a rule, in clinical practice the test is considered negative when $PC_{20}FEV_1$ is greater than 8 mg/mL (or greater than about 800 mcg in the case of $PD_{20}FEV_1$). Bronchial hyperreactivity, although it can be observed in other pulmonary or upper airway diseases and even in a small percentage of normal subjects, is present in the vast majority of patients with coughs of asthmatic origin [41]. The negativity of the bronchostimulation test with methacholine virtually excludes a diagnosis of cough of asthmatic origin. In fact, studies [12, 15] have shown that the negative predictive value of the bronchostimulation test is almost 100%; on the contrary, the positive predictive value ranges from 60 to 82%. This is due to the fact that bronchial hyperreactivity is not only present in asthmatic patients but can also be caused by other conditions, such as viral infections of the upper airways, cystic fibrosis, gastroesophageal reflux disease and chronic obstructive pulmonary disease. Irwin and collaborators [39] have demonstrated that the positivity of the bronchostimulation test with methacholine can be considered diagnostic for coughs of asthmatic origin only if it is associated with the disappearance of symptoms after therapy with bronchodilators and anti-inflammatories. In cases where the clinical history suggests the presence of cough caused by bronchial asthma, but it is not possible to perform respiratory function tests and bronchostimulation, it is advisable to prescribe bronchodilator and anti-inflammatory drugs for inhalation use and then evaluate the clinical response [39].

As a rule, in patients with typical moderate to severe asthma, respiratory function tests show the presence of airway obstruction. In these patients, the evaluation of bronchial hyperreactivity obviously has no diagnostic value. Rather, the reversibility of the bronchial obstruction after administration of a bronchodilator should be assessed. An increase in forced expiratory volume in one second (FEV_1) equal to 12% of the base value and greater than 200 mL in absolute value is considered diagnostic for bronchial asthma [1]. In patients with airway obstruction who do not respond to a single administration of bronchodilator, the increase in FEV_1 achieved after 2–4 weeks of treatment with inhaled bronchodilators and high-dose corticosteroids administered orally or by inhalation can be evaluated.

Evidence for airway eosinophilic inflammation can be sought by performing differential cell counts on samples from sputum induction or bronchoalveolar lavage. In such cases, elevated eosinophils (>3%) in the airways in the absence of BHR (Bronchial hyperreactivity) would suggests EB (eosinophilic bronchitis), which has been reported in up to 13% of patients attending cough clinics [41]. However, most centres do not have such facilities available; hence a non-invasive alternative is the use of fractional exhaled nitric oxide (FeNO) in breath or blood eosinophilia as a surrogate marker to assess airway eosinophilia. The clinical usefulness of FeNO or blood eosinophils in aiding diagnosis or predicting treatment response in patients with chronic cough has not yet been systematically evaluated [42].

A meta-analysis of observational studies showed exhaled nitric oxide to have a relatively high specificity of 0.85 in predicting asthma among adult patients with chronic cough [43]; however, there is still no consensus on the cut-off level for the

diagnosis. Blood eosinophilia is a simple and readily available measure, but is characterised by diurnal and seasonal variability [44] so multiple assessments should be made [45]. An eosinophil count of greater than 0.3 cells/μL may be taken to indicate eosinophilic airway inflammation [46, 47].

7.8 Therapy

As a general rule, pharmacological treatment of coughs of asthmatic origin involves the use of medications that prevent or reduce airway inflammation and medications that prevent or reduce bronchial obstruction.

The main anti-inflammatory drugs are corticosteroids, chromones (disodium cromoglicate, nedocromil sodium) and antileukotrienes, while the first choice bronchodilators in the treatment of bronchial asthma are those of beta-adrenergic type with short and long duration of action. Other bronchodilator drugs less frequently used in the treatment of forms of bronchial asthma are anticholinergics and theophyllines. Since asthma is the expression of a localised airway disease, both anti-inflammatory and bronchodilator drugs are preferably used by inhalation, as they are equally effective but less frequently associated with side effects than systemically administered drugs. Corticosteroids and bronchodilators are generally administered as pre-dosed pressurised aerosols or as inhalation powders. It has now been clearly demonstrated that adequate anti-inflammatory treatment reduces the infiltration of inflammatory cells into the bronchial wall and lumen associated with a reduction in anatomical changes of the airways, preventing irreversible obstruction of the airways. The choice of pharmacological treatment to be applied in each individual case derives essentially from defining the severity of the disease. In patients with intermittent coughing, the symptom can be controlled by administration of short-acting inhaled beta-adrenergic bronchodilators. When tussigenic symptoms occur more frequently and no longer respond to treatment with bronchodilators alone, it is necessary to use inhaled corticosteroid anti-inflammatory drugs. Sometimes, in the case of severe exacerbations of symptoms, it may be appropriate to initially prescribe a cycle (10–14 days) of oral corticosteroid drugs associated with inhaled bronchodilators; subsequently, inhaled corticosteroids may be used as maintenance therapy. The maximum effect of treatment with inhaled corticosteroid drugs is not achieved before 6–8 weeks [11].

Once cough reduction is achieved, the dosage of these drugs can be gradually reduced. It is important to underline that the reduction or suspension of anti-inflammatory treatment often leads to the reappearance of signs of inflammation in the airways and therefore to a resumption of the disease. The time between the suspension of treatment and the reappearance of the cough is, however, variable and, in some cases, the cough may not reappear.

Disodium cromoglicate or sodium nedocromil, although having a lower anti-inflammatory power than corticosteroid drugs, also reduce the state of bronchial hyperreactivity in patients with bronchial asthma. In particular, clinical studies have shown that sodium nedocromil is effective in the treatment of asthmatic cough,

resulting in a significant reduction in the frequency of coughing in patients with mild to moderate asthma from the first 24 h of treatment. It has been hypothesised that this drug exerts its antitussive action not only by inhibiting the release of mediators from inflammatory cells, but also by partial inactivation of tussigen receptors in the airways [48].

Antileukotrienes are a category of anti-asthmatic drugs with anti-inflammatory action. Numerous in vitro and in vivo studies have demonstrated the efficacy of these drugs in reducing markers of asthmatic inflammation and in inhibiting bronchoconstriction induced by numerous stimuli. In addition, many clinical studies have shown that the use of these drugs allows you to reduce the dosage of inhaled corticosteroids without significant changes in disease course.

There is a need for practical tests for predicting anti-inflammatory treatment responses in patients with chronic cough. However, there is a still lack of quality evidence.

Randomised placebo-controlled trials are required to validate the utility or otherwise of FeNO as a predictor of treatment response in chronic cough patients. Currently, there is no study examining the predictive utility of blood eosinophils in patients with chronic cough.

Given the uncertainty of diagnostic testing, a therapeutic trial may be indicated for asthmatic cough. In adults oral prednisolone for 1 week may cause a dramatic decrease in cough [49]. Inhaled corticosteroids (ICS) may be used when oral is contraindicated and is preferable in children. However it may be less effective since inflammation in CVA and EB is located in different parts of the airway from that seen in classic asthma [50]. This also may explain the greater efficacy of systemic leukotriene antagonists such as montelukast in asthmatic cough [51].

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Chronic Cough During Gastro-oesophageal Reflux

8

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8.1 General Aspects

In all age groups, gastro-oesophageal reflux disease (or, more briefly, reflux disease) is considered a major cause of chronic cough. It is the third most common cause of chronic cough in both children [1, 2] and adults [3–5], and the second most prevalent cause of chronic cough in the elderly [3].

In non-smoking patients with normal chest X-ray who are not taking cough-inducing drugs (e.g. ACE inhibitors) and in whom the diagnosis of asthma and/or upper airway cough syndrome has been reasonably excluded, gastro-oesophageal reflux should be considered as the most likely cause of chronic cough [2–5]. Numerous studies have also shown that chronic cough can have multiple and concomitant causes [2, 5]. For this reason, reflux should be considered a possible cause of coughing in patients who responded only partially to treatment for asthma and posterior rhinorrhoea.

In addition, coughing may be the only symptom during reflux disease, i.e. the symptom of disease onset [4]. A recent pilot study [6] has suggested that proton pump inhibitor therapy is beneficial in patients with unexplained chronic cough even in the absence of reflux evidence. More frequently, reflux coughing is associated with specific symptoms caused by lesions due to acidic exposure in the oesophagus.

Numerous clinical investigations have established that reflux disease appears to be the factor responsible for chronic cough in a percentage of cases ranging from 2 to 24% [2–5, 7]. In addition, anti-reflux treatment has been shown to effectively

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control chronic cough in 14 out of 20 patients in whom a definitive cause of the symptom could not be established [8]. There is, however, disagreement: some authors [9], in fact, have not identified any correlation between episodes of reflux revealed with oesophageal pH meter tests and the onset of coughing. Nevertheless, most clinical investigations show a clear relationship between reflux and coughing [4, 9, 10]. It is also important to remember that chronic cough can have several concomitant causes: Irwin et al. [4] demonstrated that reflux disease, asthma and posterior rhinorrhoea were present simultaneously in 59% of a group of 88 patients with persistent cough.

8.2 Pathophysiology

The exact mechanism by which the gastro-oesophageal reflux can evoke cough reflux is unclear. On the basis of clinical and experimental evidence, two distinct but not mutually exclusive mechanisms are considered to be involved. It is believed that the gastric content returned to the oesophagus may be partially aspirated, causing chronic irritation of the more proximal segment of the respiratory tract, in particular the larynx. If the phenomena of micro- or macro-aspiration of the gastric content involve the gastric content penetrating until it affects more distal segments of the respiratory tract, the cough can be determined by inflammation or infection of the trachea and/or large bronchi. Alternatively, it seems that simple prolonged acid exposure of the oesophageal mucosa may result in reflex respiratory responses, such as bronchospasm, cough, dyspnoea and hypersecretion of mucus, by stimulating vagal receptors in the oesophageal mucosa [3]. Furthermore, it has been shown that in chronic cough patients with coexistent acid reflux the airway level of substance P and neurokinin A are increased, suggesting airway sensory nerve activation facilitating cough in this population [11].

As illustrated elsewhere in this book, both the larynx and the intra-thoracic airways are richly innervated by sensory fibres that are certainly involved in the genesis of the cough reflex [12]. The oesophagus is innervated by both vagus and spinal nerves. Most of the sensory fibres that make up the vagal and spinal afferents belong to pseudounipolar cells located, respectively, in the nodose ganglion and in the dorsal root ganglion. These sensory fibres innervate the serosa, the smooth longitudinal and annular muscle cells, and the mucous membrane of the oesophagus. The sensory endings located at the level of the oesophageal mucosa are highly sensitive to mechanical stimulation, while their chemical sensitivity, particularly to pH changes, is contentious. The mechanical and chemical responsiveness of vagal afferents originating from oesophageal receptors has recently been analysed by Sekizawa et al. [12] in anaesthetised and paralysed dogs. In response to oesophagus distension, most of the receptors studied had a slow-adapting discharge similar to that of stretch receptors located in the airways. A small part of the receptors, on the other hand, presented, in response to the same type of stimulation, a fast-adapting discharge, similar to that characteristic of the "irritant receptors" of the airways [12]. The most surprising result illustrated in this study by Ing et al. [13] concerns the

responsiveness of the distal oesophagus in 22 patients with chronic cough and reflux and in 12 healthy controls. Acidic stimulation of the distal oesophagus caused coughing in patients with chronic cough and reflux, while it proved ineffective in control subjects. Infusion of lidocaine into the distal oesophagus and inhalation of ipratropium bromide, an anticholinergic agent capable of blocking the bronchospastic response, reduced or blocked the cough response. Inhibition of acid-induced cough following topical application of lidocaine was likely to result from inactivation of oesophageal receptors putatively involved in reflex mediation. Inactivation of the reflex by an anticholinergic agent administered by inhalation implies a more complex mechanism of action. Since anticholinergic drugs act by blocking bronchoconstriction and mucus secretion mediated by efferent vagal fibres, the results of Ing et al. [13] study suggest that coughing induced by acidic stimulation of the oesophagus could be, at least in part, a side effect of other reflex responses, such as bronchoconstriction and/or mucus secretion [14]. Indeed, bronchoconstriction in itself represents a powerful tussigenic stimulus [15].

Notably, the presence of acidic substances in the gastric content is not the only potential stimulus for oesophageal receptors during reflux episodes; other constituents of gastric secretions, such as pepsin and trypsin, may be even more damaging agents for the oesophageal mucosa. In normal conditions, the pH value in the oesophageal lumen is approximately 7, falling to less than 4 during an episode of reflux. Reflux episodes occur physiologically, especially after food intake, but do not result in clinical signs in healthy individuals. The best indicator of pathological reflux is the total time of acid exposure with pH below 4 [16]. The upper limit of the total time of acid exposure at the level of the distal oesophagus is between 5 and 7% [8]. Gastro-oesophageal reflux takes on pathological characteristics when signs or symptoms of epithelial damage to the digestive and/or respiratory tract are determined. In patients with chronic cough that is thought to be caused by reflux, the number and duration of reflux episodes, the total time of acid exposure, and the temporal relationship between the onset of coughing and reflux episodes should be established. Irwin et al. [9] observed that in patients with chronic reflux cough, the number of coughs was related to the number of reflux episodes, the duration of the most prolonged episode, and the fraction of time during which oesophageal pH remained below 4. Unfortunately, these phenomena are not uniformly observed in all patients with reflux cough. Some individuals with reflux cough have a normal number of reflux episodes during the day and a period of oesophageal exposure at pH below 4 of normal duration [8]. In some patients, the only significant finding is the correlation between an episode of reflux and the onset of coughing [8]. Reflux can reasonably be held responsible for coughing in patients who, despite having normal reflux parameters, show a precise temporal relationship between the onset of coughing and objectively documented episodes of reflux. Even in the absence of precise temporal relationships between coughing and reflux, the latter cannot be ruled out as the case. In a study conducted on 15 patients with chronic coughs of unknown origin, it was demonstrated that the relationship between episodes of reflux and onset of cough could only be established in 9% of cases [16].

8.3 Clinical Manifestations

Patients with reflux cough often report that the symptom has lasted for months or years. Although reflux coughs are considered to be typically non-productive, this is only true in 50% of cases, while in 16% of cases cough can be accompanied by abundant mucus secretion (>60 mL/day). Hypersecretion of mucus during reflux cough may be induced by different mechanisms, besides inflammation or infectious episodes secondary to aspiration. Studies in animal models [17] have in fact shown that acid-related irritation of the oesophagus can cause mucus secretion in the respiratory tract through a reflex mechanism of vagal origin. In the case of aspiration episodes, the cough is frequently associated with clinical signs of tracheobronchitis with fever, bronchospasm and purulent sputum.

It is commonly believed that reflux coughing occurs more frequently at night or when the patient is supine. Although lying down facilitates reflux for obvious gravitational reasons, studies aimed at ascertaining this possibility have shown that coughing at night can be equally frequently detected in patients with posterior rhinorrhoea [18] and, due to the known phenomenon of vagal hypertension at night, in patients with bronchial asthma. In addition, Irwin et al. [19] have shown that reflux coughing actually occurs more frequently during daylight hours, when the patient is awake and upright. The fact that there may be no history of coughing at night should not dissuade us from considering reflux as a potential cause of coughing. During sleep, coughing usually occurs less frequently, as the reflex is inhibited [20, 21]. If the tussigenic stimulus is of adequate intensity, the patient wakes up and, in rapid succession, the cough ensues.

Notably, the typical symptoms of reflux are frequently absent in patients with chronic acid-related cough; this absence should therefore not dispel the diagnostic suspicion. In a significant number of cases, however, reflux cough is accompanied by the classic symptomatology of the underlying disease: retrosternal burning, regurgitation, perception of bitterness in the mouth [19]. Coughing is frequently associated with chest pain, globus sensation, nausea, bronchospasm, laryngeal stridor, dental erosion, hoarseness and pain in the pharynx [19, 22, 23]. Importantly, it has been established that chronic cough may be the sole presenting symptom of reflux [24].

Patients with predominantly extra-oesophageal manifestations of reflux such as hoarseness, dysphonia, globus, dysphagia and chronic cough may lack the typical oesophageal manifestations of reflux such as heartburn and regurgitation; they are often misdiagnosed as having an upper airways cough syndrome due to some clinical condition affecting the nasal airways and sinuses. It is now becoming widely appreciated that this cohort of symptoms may represent the clinical manifestation of laryngopharyngeal reflux (LPR), a process by which gastric contents affect the extraoesophageal structures of the head and neck [25].

8.4 Diagnosis

A diagnosis of chronic reflux cough can be difficult to establish with the help of clinical and medical history signs alone, unless they have the peculiar characteristics mentioned above. The characterisation of the cough is also of little or no use: crises of paroxysmal cough, "barking", postprandial, nighttime, dry or productive cough can equally be triggered by episodes of reflux or by factors of different origin.

8.4.1 Double Contrast Oesophagoscopy

The double-contrast oesophagography method has been widely used in the diagnosis of gastro-oesophageal reflux disease. This method highlights the occurrence of reflux phenomena, but cannot establish a relationship between reflux phenomena and coughing.

8.4.2 Endoscopic Examination of the Oesophagus

Oesophageal endoscopy is another method to reveal the presence of reflux-related lesions of the oesophageal mucosa and to detect, in some circumstances, imperfect function of the lower oesophageal sphincter. As with double-contrast oesophagography, endoscopy does not allow a cause-effect relationship between oesophageal lesions and cough to be established.

8.4.3 Bernstein Test

The Bernstein test is another diagnostic option. The test consists of instilling saline or a hydrochloric acid solution into the oesophagus and is considered positive when the oesophageal or extra-oesophageal symptoms, including coughing, can be reproduced by administering acid but not saline. Although the test is frequently positive in patients with reflux disease, triggering the typical oesophageal symptoms in these patients, it has provided disappointing results in the diagnosis of acid-related symptoms such as chest pain, nausea and cough.

8.4.4 Oesophageal pH Meter

Prolonged monitoring (at least 24 h) of oesophageal pH seems to be the most effective method for diagnosing reflux disease. The technique consists of introducing a catheter into the oesophagus, the end of which is equipped with an electrode sensitive to pH variations, which is generally placed 5–6 cm above the gastro-oesophageal junction. The electrode is connected to a system that records the amplitude of pH

changes, the number and duration of reflux episodes and, by means of a special event marker device, to indicate, on the part of the patient, the precise moment in which typical or atypical reflux symptoms such as retrosternal pain or burning, coughing, bronchospasm, chest pain, etc. occur. The possibility of objectively establishing a temporal relationship between episodes of reflux and the appearance of symptoms perceived by the patient appears to be of great importance for diagnosing the onset of reflux cough. More precisely, a causal relationship effect between episodes of reflux and onset of coughing is most likely when the following conditions occur:

- The onset of coughing is related to episodes of reflux.
- More than 4 episodes of reflux lasting longer than 4 min occur within 24 h.
- The percentage of time during which the oesophageal pH remains steadily below 4 exceeds 4.4% of the total time.
- The total number of reflux episodes is greater than 50.

Caution should be exercised in establishing a relationship between reflux and coughing when the former events are very high in number and long-lasting and only sporadically associated with the onset of coughing. In this condition, in fact, the association between cough and reflux can be completely random and, consequently, can be established with certainty only if anti-reflux therapy is successful.

An alternative but reasonable and widely used diagnostic approach may be the evaluation of results obtained by empirically prescribing an anti-reflux therapy cycle. This approach is particularly suitable when no diagnostic resources, such as oesophageal pH meter, are available. Empirical anti-reflux treatment must be continued for at least 3–4 months before it can be declared ineffective [3]. In any case, confirmation of the presence of gastro-oesophageal reflux should be obtained, preferably by means of oesophageal pH meter, as soon as possible. It can be difficult to convince the patient that they have a reflux cough without specific symptoms and objective confirmation of the disorder; on the other hand, since the pH meter has a high negative predictive value, documenting the absence of reflux can avoid unjustified and prolonged use of very expensive drugs.

8.4.5 Pepsin Test

It detects pepsin in expectorated saliva and is established as a simple, non-invasive measure of reflux of gastric contents. It has been used to detect pepsin A in patients with both gastro-oesophageal reflux disease and extra-oesophageal reflux into the laryngopharynx and airways [26].

8.4.6 Deflation Cough

Some patients exhibit cough-like expiratory efforts (“deflation cough”) during slow or forced vital capacity manoeuvers [27, 28]. These patients also presented

an association between chronic cough and symptoms of gastro-oesophageal reflux. Interestingly, prior administration of an antacid preparation effectively blocked the coughing evoked by maximal lung emptying [28]. Subsequent lines of evidence have demonstrated that *absence* of deflation cough in patients with chronic cough and reflux symptoms reliably rules out acidic reflux as the cause of cough and points to other possible causes of cough including non-acid reflux [29].

8.5 Therapy

The therapy for reflux disease and, consequently, the symptoms related to it requires both changes in lifestyle and administering appropriate drugs. Occasionally, surgery may be necessary to correct the basic disorder. Often reflux cough generally responds very slowly to treatment and may take several weeks/months of treatment to achieve significant improvements [3].

8.6 Changing Life Habits

In general, the patient should be encouraged to avoid eating foods, drinking beverages and adopting postures that induce reflux. Chocolate, mint, onion, coffee, tea, coke and citrus fruit juices seem to be particularly effective reflux inducers. Similar considerations apply to certain pharmacological agents such as, for example, anti-inflammatory drugs. Reduced intake of fats and a diet with a high protein content seems to decrease the number and intensity of reflux episodes. The patient should be encouraged to avoid lying down after meals and to correct any excess weight and stop smoking. Nicotine, in fact, decreases the tone of the lower oesophageal sphincter. Lifting the head of the bed (15–20 cm) may result in a reduction in the number and duration of nighttime reflux episodes. These episodes can have negative effects, as some of the mechanisms that protect the oesophagus from acid exposure are inactive during sleep. In the supine position, the advantages of gravity that are guaranteed by being upright cannot be taken advantage of. During sleep, oesophageal peristalsis is reduced, as is the production of saliva that, having a pH of 6.8–7.4, may play a buffering effect. The results produced on reflux cough by a mere change in life habits have not been studied systematically. There are, however, numerous investigations that have evaluated the results obtained by associating lifestyle changes with the intake of histamine H_2 receptor inhibitor drugs (H_2 blockers), proton-pump inhibitors and prokinetics [30–36].

Although a comprehensive review of the proposed guidelines for the treatment of reflux disease is far beyond the scope of this book, we feel it appropriate to include a short list of the most commonly used pharmacological agents, with special reference to their effects in controlling secondary and reflux cough.

8.7 Antacids and Alginic Acid

The use of "as needed" antacids is widespread and represents a safe and effective method for the resolution of mild to moderate gastric heartburn. Antacids act by neutralising the acidity of gastric secretions, but their duration of action is short.

Alginic acid, often used in combination with antacids, interacts with saliva to form a highly viscous solution that acts as a mechanical barrier "floating" above the gastric content. This barrier reduces the number and intensity of reflux episodes, but is not active when lying down.

8.8 H_2 Blockers

The action of H_2 blockers is reducing the volume of gastric secretion, and at the same time reducing the content and concentration of hydrogen ions. Approximately 75% of patients with reflux cough have significant symptom improvements after treatment with H_2 blockers, alone or in combination with prokinetics. H_2 blockers are thus considered by some to be the first-choice drug for reflux disease and related symptoms.

8.9 Proton-Pump Inhibitors

Proton-pump inhibitors act by blocking an enzyme (H^+/K^+ ATPase), which is produced only by parietal cells in the gastric mucosa. Proton-pump inhibitors are actually prodrugs that in a neutral pH environment have no inhibitory power. They are administered in gastro-resistant capsules that allow absorption of the drug only in the intestinal tract. Once absorbed, it reaches the secretory channels of the parietal cells where it is "activated" by the presence of H^+ ions. Once activated, the drug is capable of blocking the proton pump in a dose-dependent manner.

The pharmacological action of this class of drugs entails inhibition of acid secretion without significant effects on the reduction of the overall volume of gastric secretion and pepsin; they do not significantly affect gastric motility. A modest increase in gastric secretion comes as a consequence of the deep inhibition of gastric secretion. In experimental animals, in fact, prolonged administration of very high doses of omeprazole causes hyperplasia of parietal cells, probably due to the trophic effect of gastrin on this type of cells. Prolonged administration (up to 6 years) of therapeutic doses of omeprazole does not result in proliferative alterations of parietal cells in humans.

Proton-pump inhibitors have been shown to be effective in the treatment of reflux disease. In particular, these agents have been shown to be significantly more effective than H_2 blockers in treating erosive lesions of the oesophageal mucosa and in relieving reflux-related symptoms [34]. Kamel et al. [32] evaluated the role of empirical treatment with omeprazole in a group of patients with reflux associated with posterior laryngitis. The patients had a wide range of acid-related symptoms, both oesophageal and extra-oesophageal, including chronic cough. Treatment with

omeprazole (40 mg/day) proved to be completely effective in controlling oesophageal and laryngeal symptoms in 14 of the 21 patients examined. In seven patients, however, the improvement was only partial, even after doubling the dosage of omeprazole. These results indicate that empirical treatment with omeprazole is a reasonable therapeutic approach in patients with reflux disease associated with oesophageal and extra-oesophageal symptoms. A subsequent study [33] showed that patients with reflux oesophagitis have a high sensitivity to experimentally inhaled tussigenic stimuli, and that this sensitivity is significantly reduced after prolonged treatment with omeprazole. Ours et al. [34] showed that coughing occurs in 26% of patients with reflux disease and that prolonged administration of omeprazole (up to 1 year) leads to clear improvements in the symptom until it disappears. It is interesting to note that in 11 patients with secondary reflux asthma treated with omeprazole for 4 weeks, no significant improvement in respiratory symptoms was observed [35]. This suggests that the treatment of respiratory symptoms during reflux disease requires prolonged therapies that allow the complete resolution of the lesions produced by acid exposure at the level of the oesophageal mucosa, or, where appropriate, the upper airways.

In keeping with the possibility that neurogenic airway inflammation plays an indirect role in reflux cough, Takeda et al. have recently demonstrated a reduction in sputum and plasma levels of substance P and sputum neutrophil count following symptom-effective treatment with rabeprazole, a last generation PPI, in patients with reflux cough [36].

8.10 Prokinetic Agents

Prokinetic agents, such as domperidone and cisapride, are widely used in the treatment of reflux disease as they cause a modest increase in the tone of the lower oesophageal sphincter and significantly promote gastric emptying.

Although the use of prokinetic drugs in combination with H_2 blockers and an anti-reflux diet has been shown to be useful in the treatment of reflux cough [37], the separate role played by these agents is not clearly identifiable, at least in adult patients. On the contrary, there are numerous paediatric studies in which the efficacy of prokinetics administered in monotherapy for the treatment of reflux cough emerges clearly. In a group of 19 children with secondary reflux bronchopulmonary disease, it was demonstrated that the use of cisapride (0.3 mg/kg) significantly reduced the number and duration of reflux episodes, the total time period for which the oesophageal pH was exposed to values below 4, and the frequency and intensity of night cough bouts [37].

8.11 Surgical Therapy

The most commonly used surgical methods for the resolution of reflux disease forms refractory to pharmacological treatment include gastric fundoplication around the lower end of the oesophagus (Nissen and Belsey methods), as well as the Hill

repair posterior gastropexy, by means of which the axis or relative position of the gastro-oesophageal junction is modified. Surgery is believed to be more effective than medical therapy in preventing the reappearance of the signs and symptoms of reflux disease [38], especially in patients with preserved oesophageal motility [39]. With specific regard to reflux cough, surgery, in this case fundoplication, has proved effective in 95 of 129 consecutive patients [40].

Even in the case of surgical therapy, the improvement or disappearance of respiratory symptoms is usually a late phenomenon, which occurs completely several weeks or months after surgery. As previously mentioned, this phenomenon suggests that the disappearance of symptoms occurs only after the complete resolution of lesions caused by acid exposure.

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Clinical Methods for the Study of Cough

9

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9.1 Introduction

In the last 30 years, there have been considerable advances in our understanding of the mechanisms and management of cough. Basic science has combined closely with clinical practice and the pharmaceutical industry to develop new diagnostic and therapeutic strategies. However, the management of cough remains a challenge for the clinician [1]. In both Europe [2] and North America [3] guidelines have now been drawn up and recommendations made on the management of cough. Chronic cough can be differentiated from acute cough by a cut-off of 8 weeks [2, 3]. Although arbitrary, this distinction is helpful in clinical practice as the aetiology and epidemiology of chronic cough are quite different from those of acute cough. While a wide range of diseases may be associated with chronic cough, it has become increasingly clear that the majority of adult patients presenting with chronic cough as the primary complaint have a common clinical presentation [2]. They often complain of exquisite sensitivity to inhalation of environmental irritants such as perfumes and cold air, which result in sensations of irritation in the throat and an urge to cough, features suggestive of heightened sensitivity of the neuronal pathways mediating cough [4]. These observations have led to the concept of cough hypersensitivity syndrome as a diagnosis [4, 5].

The assessment of cough by the clinician should include both tools that measure the amount and severity of the cough, as well as investigations that may lead to unravelling the cause of the cough, in terms of both disease and disease processes. An anatomical approach to the investigation of the patient with chronic cough has been successfully advocated [3, 4], and many investigations that are part of the workup of the patient with persistent cough contribute to this approach. However, not only

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Table 9.1 Cough measurement and monitoring tools

Subjective tools
• Visual analogue scale (VAS)
• Cough severity diary
Cough-related quality of life measures
• Leicester cough questionnaire
• Cough-specific quality of life questionnaire
Cough recording monitor
• VitaloJak
• Leicester cough monitor
Cough inhalation challenges
• Capsaicin
• Citric Acid
• Ultrasonically nebulised distilled water
• Tartaric acid
• Cinnamaldehyde
• Bradykinin
• Adenosine triphosphate

anatomical evaluation but also assessing cough severity must be part of the investigation. The assessment of cough severity is important for evaluating the response to therapy [6]. The severity of cough can be measured in several aspects (symptom severity, frequency, intensity and impact on quality of life), and a number of subjective and objective validated tools are now available to assess cough (Table 9.1). The importance of a combined subjective and objective assessment for comprehensive evaluation of cough has been advocated in the recent European Respiratory Society guidelines on the assessment cough [2]. This chapter will describe subjective and objective clinical methods for assessing and monitoring cough.

9.2 Subjective Methods for Assessing Cough

Cough severity can be measured in several ways but the clinician can simply ask the patient how the cough affects his or her daily living and activities, the frequency and intensity of episodes of cough, and his or her own appreciation of the overall severity, and thus obtain a subjective evaluation of the patient's perception of this symptom. Early clinical studies assessed cough severity by using symptom score scales ranging from mild to severe or patient's diaries [7, 8]. Although this is the most convenient tool that the clinician has to assess severity of cough, it remains a relatively unvalidated measure.

9.2.1 Visual Analogue Scale (VAS)

Visual analogue scales are widely used for the subjective assessment of cough because they are easy to use and freely available [9]. Patients mark a point on a straight line corresponding to their perception of the severity of cough. The score ranges from 0 to 10 cm, with 0 representing "no cough" and 10 "the worst cough

severity". The advantage of VAS is that they assess the symptom in isolation and reflect the severity and the urge to cough [9, 10]. However, it still lacks published data reporting its validity; in addition, the minimal important difference (MID) has been reported for acute [10] but not chronic cough. Nonetheless, the VAS is highly sensitive to change [9]; thus, its use should be encouraged because it is familiar to clinicians, and clinically meaningful.

9.2.2 Cough Severity Diary

The "Cough severity diary" (CSD) is a seven-item daily diary asking patients to rate their cough severity along three dimensions identified during patient focus groups and interviews that formed the basis of the diary: frequency (three items), intensity (two items) and disruptiveness (two items) [11]. The CSD has a 24-h recall period and responses to items are entered on an 11-point scale ranging from 0 to 10 with anchors on each end (e.g. never to constantly). Higher scores indicate greater severity. The CSD total score, representing the magnitude of cough severity, is calculated by averaging across all seven items; subscale scores are computed by taking the average across items comprising the given subscale [11]. The CSD has shown evidence of content validity, construct validity and reliability, and as a result may be more responsive to change. Furthermore, unlike a single-item VAS, the CSD can be used to determine which aspect of cough severity was affected by treatment [11]. There is, however, little clinical experience with this tool and the MID has not been studied.

9.3 Cough-Related Quality of Life Measures

Cough can have a wide-ranging impact on the patient, and is very disruptive. It can lead to physical symptoms such as syncope, chest pain, urine incontinence, vomiting, headache and sleep disturbance. It is associated with psychological morbidity such as anxiety and depression and socially it can lead to embarrassment and disruption of activities [12]. The impact of cough on health-related quality of life can be quantified by using specifically designed questionnaires [13]. Their advantage in comparison to VAS score is that they capture the wider impact of cough on the individual, and furthermore provide a structured and standardised approach to quantifying health status. They are well validated for this purpose and highly responsive to change [13]. The two most widely questionnaires for adult patients with chronic cough are the Leicester cough questionnaire [14] and cough-specific quality of life [15]. For children, a recently validated questionnaire—the paediatric cough-quality of life questionnaire—is now available [16].

9.3.1 Leicester Cough Questionnaire (LCQ)

The LCQ is the most widely used of all cough-related quality of life questionnaires. It consists of a 19-item questionnaire comprising three health domains: physical, psychological and social [14]. Originally developed for patients with chronic cough,

it has also been validated for patients with chronic obstructive pulmonary disease (COPD), bronchiectasis and acute cough [17, 18, 20]. The LCQ is translated into a wide range of languages and is well validated with very good internal reliability, repeatability and responsiveness [14]. The MID in acute and chronic cough are 2.0 and 1.3, respectively [20, 21].

9.3.2 Cough-Specific Quality of Life Questionnaire (CQLQ)

The CQLQ is a 28-item questionnaire with 6 domains validated for both acute and chronic cough [15]. It has good internal reliability, repeatability and responsiveness, and the MID in chronic cough is 13 units [22]. It has recently been used in clinical trials investigating the effects of proton pump inhibitors in chronic coughers [23] and Thalidomide in patients with cough associated with idiopathic pulmonary fibrosis [19].

9.4 Cough Frequency Monitors

The quantitative recording of cough events over a representative period is necessary for the objective evaluation of cough associated with different diseases and for the assessment of the efficacy of different treatments for chronic cough. Cough frequency assessment is now considered the gold standard for the objective assessment of cough [2]. Early monitors recorded the coughs onto a tape recorder either fixed on the wall of the patient's room or placed in close contact to the patients' throat [24, 25]. These monitors, however, were limited by the recording capacity of tape recorders and poor battery life [24, 25]. The development of recorders overcame hardware limitations, and therefore the focus turned to the development of software for automated cough detection. However, discrimination of cough sounds from throat clearing, speech or other noises remains difficult and some cough monitors have insufficient accuracy for cough detection, thus limiting their use in clinical practice [26]. It is worth noting that there is no system commercially available for ambulatory cough monitoring for clinical use. The VitaloJak and the Leicester cough monitor are the most widely used cough monitoring systems in clinical trials. Both systems have demonstrated good validity but they differ in their approach to cough detection: the VitaloJak requires manual assessment of condensed cough recordings, and the Leicester cough monitor is largely automated.

The relationship between objective cough frequency and subjective measures of cough such as VAS or cough-related quality of life measures is mild to moderate [27]. This indicates that the cough scoring system may also reflect other parameter than just the cough numbers, such as the perception or the physical effects of cough. The poor relationship between the results of cough scoring systems and the cough numbers detected by cough monitors does not imply that cough frequency monitoring is inaccurate for the detection of cough. Generally, the accuracy of automated cough monitors is established by comparison to manually counted recordings [28].

Cough frequency can be assessed by cough monitors during daytime, night-time or 24 h, and expressed as absolute counts or as cough numbers per hour. Some

authors suggest to express change in cough frequency as a percentage or fold change, rather than absolute change, since it has a wide range. In acute cough, the MID for cough frequency has been reported as a 54% reduction [10].

The analysis of cough counts by means of cough frequency monitors has showed that patients with chronic cough on average cough every 2 min in a 24-h period, whereas healthy subjects cough on average every 30 min [27]. Most of the coughs of patients with chronic cough occurred during the awake hours, with reduced or little activity during sleeping hours [29]. This is in agreement with studies showing a depression of the cough reflex during rapid eye movement sleep [30]. In patients complaining of cough, the pattern and frequency of cough is very similar irrespective of underlying causes such as gastro-oesophageal reflux and cough variant asthma.

The utility of cough monitor in clinical practice has not been established yet. The severity of cough can simply be assessed by asking the patient, but the disadvantage of this is that some patients and clinicians may be poor judges of symptom severity. Cough monitors can potentially be used to validate the presence of cough, as well as to quantify the response to therapy. However, the benefits of cough monitoring technology in the clinic need further investigation.

9.5 Cough Sensitivity to Inhalation Agents

The idea of inhalation cough challenges originated from the clinical observation that even during the administration of therapeutic aerosols patients can experience a sense of irritation of the upper airways often resulting in cough. Aerosolised agents can easily be delivered to the central airways, i.e. where sensory nerve terminals are most dense, and a variety of chemical agents can be inhaled to provoke coughing experimentally. Inhalation of a tussigenic aerosol, therefore, forms the basis of cough challenge testing.

Patients with chronic cough have a hypersensitive cough reflex to a range of tussive agents, which diminishes with successful treatment [31]. Citric acid and capsaicin are the two most widely used in cough challenge testing, although others include ultrasonically nebulised distilled water and tartaric acid [31]. The methodology involved is similar to bronchial provocation testing with agents such as methacholine but, in contrast to these inhalation tests, there are not yet any standards agreed for the methodology, which tend to be laboratory specific making comparisons between studies difficult [31]. Despite these methodological issues, inhalation cough challenges permit to evaluate both the sensory and motor components of the cough reflex, and may provide an index of cough severity in patients with chronic cough.

9.5.1 Cough Sensitivity

The most convenient method for assessing cough sensitivity to inhalation of tussigenic agents is the measurement of cough threshold. This can be defined as the lowest concentration of an agent causing at least one cough effort [32] or a predetermined (generally 2 and 5) number of expiratory thrusts [31]. Typically, the

concentrations of a tussive agent inducing 2 (C2) or 5 (C5) coughs are taken to be the first administered dose inducing 2 or more and 5 or more coughs, respectively [33]. Differing opinions exist among investigators regarding which is the more highly reproducible measurement [31]. Several studies report both values but not infrequently only C5 is reported. Some authors [34] consider C5 of clinical superior value than C2 while others [35] found C2 to be more reproducible. In our laboratory, cough threshold to distilled water (fog) aerosol is defined as the concentration lowest fog concentration capable of evoking at least one cough effort during two inhalation periods, each lasting 1 min, and separated by a 30 min interval [32]. The short- and long-term repeatability of our methodology to assess cough threshold values in humans has been demonstrated [36, 37].

9.5.2 Cough Motor Response

In most challenges, the cough response is assessed in terms of cough frequency. Although the measurement of this variable has the undeniable advantage of being inexpensive and relatively easy to assess, it is unclear whether it reflects cough sensitivity, the intensity of the evoked motor response, or both. Furthermore, the reproducibility of cough threshold measurements has been shown to be subjected to the experimental conditions. Trials specifically designed to evaluate also the reproducibility of cough frequency during fog challenges demonstrated a low degree of repeatability in response to stimuli of threshold intensity [36]. Conversely, for stimuli of supra-threshold intensity, cough frequency measurements displayed a higher degree of repeatability [36]. The intensity of cough can adequately be quantified by recording cough expiratory flow [38]. The airflow generated by a subject during voluntary and reflex cough efforts can easily be recorded by means of a large-size pneumotachograph. Several variables that may be important for assessing the intensity of a cough effort can be measured or calculated from a cough flow tracing. These include the cough peak flow, the time that elapses from the onset of flow to peak flow, i.e. the so-called time to peak, and volume acceleration, that is the ratio of cough peak flow to the time to peak [38, 39]. Cough peak flow, however, may be influenced not only by the intensity of the muscle effort produced during coughing, but also by the mechanical properties of the respiratory system, particularly airway resistance [38, 39]. Recordings of flow-related variables measured during voluntary and reflex cough efforts have not only been used to asses cough frequency in normal subjects during fog challenges [38, 39] but also to explore cough mechanics and motor pattern during voluntary and reflex coughing in patients with vocal cord palsy [40] and in patients with laryngectomy [41].

Cough intensity can also be assessed by means of the integrated electromyographic activity of the abdominal muscles (IEMG), namely the *obliquus externus* muscle, which has been shown to represent the principal expiratory force generator during voluntary and reflex coughing [32]. From IEMG recordings, it is possible to measure the peak amplitude of the IEMG activity ($IEMG_P$), and the time duration of the expiratory ramp, i.e. the cough expiratory time (T_{EC}). The ratio between these two variables ($IEMG_P/T_{EC}$) represents the rate of rise or "slope" of the IEMG

activity [32]. The $IEMG_P$ is an expression of the total number of recruited motor units and of their maximal frequency of discharge, while $IEMG_P/T_{EC}$ reflects the rate of motor units recruitment as well as the rate of increase in firing frequency [32, 38]. Both $IEMG_P$ and $IEMG_P/T_{EC}$ have been shown to be proportional to the actual tension, or force, developed by the contacting muscles [38]. It has been shown that, during coughing elicited by inhalation of progressively increasing fog concentrations, both the peak and slope of the IEMG activity correlate with the simultaneously recorded expiratory flow rate in normal subjects [38].

9.5.3 The Urge-to-Cough

Inhalation of tussigenic stimuli, either acidic or non-acidic, may stimulate cough and result in a sensation of airway irritation termed as the "Urge-To-Cough" [42]. The Urge-To-Cough (UTC) sensation is a respiratory-related sensation that may involve a variety of brain regions, especially areas of the cerebral cortex [42, 43]. It has been proposed that UTC is a brain component of the cough motivation-to-action system, and its significance is based on brain mechanisms that have been described for other biological urges [42]. The role of the respiratory sensation of an UTC is to engage behavioural modulation of the cough motor action and then motivate the subject to protect the airways by coughing. The UTC can be readily measured by using standard scales such as a modified Borg category scale [42] or the visual analogue scale [44, 45]. In normal subjects challenged with capsaicin, the intensity of the UTC closely correlated with both the capsaicin concentrations and the number of elicited thrusts; furthermore, the sense of an UTC occurred before cough, thus suggesting that the cough cognitive sensory process can precede the cough motor event [42]. The slope of the log-log relationship between capsaicin concentration and UTC is a measure of the sensitivity of the subject to the cough stimulus, and the capsaicin concentration that elicits a magnitude estimation greater than zero is a measure of the cognitive threshold for the UTC [42]. Recording the motor cough response and determining the minimum stimulus concentration to elicit cough allows determination of the cough motor threshold. The relationship between the cognitive sensory and motor response to a cough stimulus allows the comparison of the threshold for the initial awareness of an UTC and the threshold for producing a cough. We showed that, in normal adults, inhalation of threshold or near-threshold fog and capsaicin concentrations evoked a variety of respiratory sensations, including UTC, that were qualitatively similar with both agents [44]. In addition, at threshold level, the intensity of the urge to cough was stronger with capsaicin than with fog, and the intensity of the sensation correlates with the cough frequency, in agreement with previous findings [42].

9.6 Conclusions

To optimally evaluate the impact of cough on patients and to assess the efficacy of cough-modifying agents, investigators ideally should use both subjective and objective methods because they have the potential to measure different aspects of

cough. For subjective assessment, the VAS is ideal for use in the clinic since it is practical, and it can be used to communicate the severity of cough to other clinicians and for longitudinal observation. It is also good for use in clinical trials. The VAS should be complemented by cough-related questionnaires to assess the impact of cough in patients' life. Cough frequency monitors are increasingly being used in clinical trials. The clinical experience of using cough monitors to date is that they are practical and valid. As for VAS, cough monitors should always be complemented by assessment of cough-related quality of life since a reduction in objective cough frequency without subjective improvement would not be considered clinically important. Despite some methodological issues, there is sufficient evidence that the cough provocation tests can detect differences in the sensitivity of the reflex in disease. These differences make the cough challenge of likely value in epidemiology studies, some aspects of clinical management and in particular in hypothesis testing. In hypothesis testing it is difficult to imagine a strategy to unravel the pathophysiology and pharmacology of the reflex without using cough challenge even if the results require validation in large studies using more clinical end-points.

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Diagnostic Approach in Adult Patients with Chronic Cough

10

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As stated elsewhere in this book, hypersensitisation of the cough reflex is a key feature in patients with troublesome chronic cough. Thus, patients typically complain from bouts of coughing triggered by low-intensity stimuli that are innocuous in the normal population. These stimuli include exposure to scents and odours, aerosols, changes in air temperature and moisture and when talking, singing or laughing [1]. Chronic cough patients may also repost a range of additional symptoms including an urge to cough, or the feeling of an itch or lump in the throat. Chocking and chest discomfort are also frequently reported. The origin of these features is uncertain; they may relate to the same process leading to cough reflex hypersensitivity or be a consequence of the underlying cause of the cough.

Since the publication of the first international cough guidelines by the American [2] and European [3] respiratory societies, the medical community has been provided with powerful diagnostic and treatment tools for the management of patients with chronic cough. The authors believe that no fundamental differences exist—in both conceptual and practical terms—among the various guidelines published so far. What follows is mainly based on the recommendations provided in 2019 by the European Respiratory Society [4]. It must be recalled that guidelines generally apply to immunocompetent patients; in those who have a compromised immune system, it will be necessary to evaluate initially the functionality of the immune system.

Medical history is the first diagnostic tool available to physicians. The collection of medical history data should consider, in addition to family predisposition to hereditary

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diseases and previous patient diseases, the habit of cigarette smoking or exposure to irritants, any factors that aggravated the cough and response to previous drug treatments. The cough duration and presence of environmental triggers must also be recorded. The impact of cough should be assessed either by recording simple measures such a cough score or a visual analogue scale (VAS); validated measures of cough quality of life such as the Leicester Cough Questionnaire are also recommended [5].

Some authors [6–8] believe that information on the mode of onset, frequency, duration and characteristics of the cough may help in defining the underlying cough causes. However, a prospective study [9] has shown that the characteristics of the cough (paroxysmal, dry or productive), the type of sound (e.g. barking or metallic) or the mode of onset (at night, during meals, induced by physical exercise) are not helpful in the differential diagnosis of the various causes of chronic cough. It is recommended cough intensity be recorded using a visual analogue scale or similar expedients.

Objective examination of the patient should not be limited to evaluating the chest, but should also consider other apparatuses. For instance, the ears (Arnold's reflex) [10] or proximal airways may be home to diseases that cause chronic cough: the detection of oedema and congestion of the nasal mucosa with the presence of hypertrophy of lymphatic follicles should lead to suspicion of posterior rhinorrhoea syndrome as a cause of coughing. In our personal experience, pain evoked by deep palpation of the epigastric region is suggestive of chronic reflux.

A clinical examination of the chest should be conducted thoroughly to highlight the presence of pathological findings that can only be detected during execution of forced expiratory manoeuvres. In this connection, it seems appropriate to recall that coughing evoked by near maximal expiration—the so-called "deflation cough"—appears to be a distinctive symptom of chronic cough related to acidic reflux [11]. Indeed, published evidence suggests that the assessment of deflation cough represents a simple and useful clinical means to suspect or exclude acidic reflux as the cause of chronic cough, even in the absence of typical oesophageal symptoms [12].

In patients with negative objective examination and taking ACE-inhibitor drugs, it is essential, before performing further diagnostic investigations, to evaluate clinical response to the suspension of these drugs. It is known, in fact, that the use of ACE inhibitors causes, particularly in female subjects, persistent cough in a percentage ranging from 6 to 14% of cases. Generally, suspending these drugs leads to the disappearance of the cough within 4 weeks [2].

A chest X-ray is the first instrumental examination to be performed in patients with chronic cough not treated with ACE-inhibitor drugs. This examination, even if some authors [2, 3] consider it to be of little use if the medical history and objective examination do not reveal any pathologies or signs of disease suggestive of a probable radiological alteration, in our opinion represents a fundamental, inexpensive and extremely useful diagnostic examination. If the chest X-ray is negative and the clinical history reveals exposure to irritants or cigarette smoke, it is advisable to evaluate first the clinical response to smoking cessation and/or exposure to the irritant. In these cases, the cough generally disappears or improves after about 4 weeks [8]. Generally, it is not advisable to perform a chest CT scan in chronic cough patients with normal chest radiograph and physical examination [4], particularly in children and females.

Spirometry is comprised among the functional tests that are required in virtually all chronic cough patients (2–4). Spirometry should be performed both before and after an inhaled bronchodilator, in order to demonstrate significant airway reversibility. If spirometry is normal, and a diagnosis of asthma is considered probable from the history, methacholine provocation tests should be performed [2–4].

If the cough is caused by posterior rhinorrhoea syndrome, bronchial asthma or gastro-oesophageal reflux disease, the patient should be given specific drug treatment and their clinical response evaluated.

If, despite treatment, the cough persists or does not improve, the doctor must consider the possibility of a cough of post-infectious origin. This is defined as a cough lasting more than 3 weeks after an infection of the upper or lower airways in the presence of normal chest radiological findings. According to some studies, this type of cough has a frequency ranging from 11 to 25%, and generally resolves spontaneously within about 4–5 weeks [2, 3, 13]. One particular case of respiratory infection that can present as a sequela to chronic cough is whooping cough, a frequent infectious disease causing chronic cough in childhood that should always be suspected, even in adult patients.

If the chest X-ray is abnormal (e.g. due to the presence of opacity, diffuse or localised infiltrates), the patient will have to undergo further investigations, to be established on the basis of the X-ray findings. Furthermore, in these cases, once the underlying pathological condition causing the cough has been identified, specific treatment must be established and clinical response evaluated.

If a patient continues to experience a persistent cough even after a full evaluation and specific treatment of the presumed cause, before diagnosing a psychogenic cough, two possibilities should be considered: (1) errors have been made during the evaluation; or (2) that the treatment established may be ineffective or inadequate. Common mistakes include:

1. Considering a positive result of the methacholine bronchostimulation test as a sign of asthmatic cough, since test is characterised by a very high sensitivity (almost 100%), but low specificity (between 60 and 80%). In fact, it is frequent to find transient hyperreactivity of the airways during and 2–4 weeks after viral infections, during airway diseases such as chronic obstructive pulmonary disease and cystic fibrosis, or gastro-oesophageal reflux disease.
2. Considering that the latest generation of antihistamine drugs are effective in the treatment of posterior rhinorrhoea caused by conditions not associated with histamine release; there are studies [2] showing that new antihistamines do not improve coughing caused by posterior rhinorrhoea, probably because of their low anticholinergic activity compared to first-generation antihistamines.
3. Not considering that there may be several causes of coughing at the same time; in fact, it is frequent to find a combination of causes in the same patient.
4. Not considering that gastro-oesophageal reflux as a cause of coughing may take up to 2/3 months of treatment before the cough improves and on average 5–6 months before it disappears.
5. Not considering the possibility that therapy with H_2 blockers alone may be inadequate in the treatment of coughing due to gastro-oesophageal reflux disease.

In a considerable percentage of patients (15–40%), the cause of cough remains undetermined despite accurate clinical and functional assessments [14]. In such cases, terms such as idiopathic chronic cough, unexplained chronic cough and chronic refractory cough have been used to describe this clinical condition [4].

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Age-Related Remodeling in Cough: What May Stand Behind

11

Ahmad Kantar

11.1 Introduction

Coughing is a complex respiratory phenomenon that occurs through the activation of the cough reflex. The evolutionary basis for reflex activation may be to prevent the harmful effects of aspiration of gastric contents into the lungs and to protect the respiratory tract from the risk of infections and irritants. In On the Origin of Species, Darwin noted "*the strange fact that every particle of food and drink which we swallow has to pass over the orifice of the trachea, with some risk of falling into the lungs… (1859, p. 191)*" [1]. Because of this peculiar anatomy, which differs from that of all other mammals, choking on food is a risk in humans. This species-specific problem seems to be a consequence of the mutations that crafted the human face, pharynx, and tongue so as to make it easier to speak and to correctly interpret the acoustic speech signals that we hear. It is now apparent that a massive epigenetic restructuring of the genes that determine the anatomy of the head, neck, tongue, larynx, and mouth enhanced our ability to talk after anatomically modern humans split from Neanderthals and Denisovans more than 450,000 years ago [2]. At birth in human infants most of the tongue is positioned in the mouth and its shape is flat as is the case for other mammals. When ingesting liquids, an infant's larynx can be raised forming a sealed passage from the nose to allow breathing while the liquid flows around the larynx. This explains why human infants can lap up milk uninterrupted by breathing. A complex developmental process that spans the first 8 years of life takes place in humans to arrive at adult-like morphology [3]. These changes facilitate speech communication, compensating for increasing the risk of choking.

Nervous systems control physiological processes essential for survival, and at the same time interface animals with their changing environment. Recent advances in genomic and molecular biology techniques applied to brain research have

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provided exciting insights into how complex behaviors are shaped by selection of novel brain pathways and functions of the nervous system [4, 5]. Evolution has many ways to tinker with the anatomy and physiology of a neural circuit: connections between neurons can be added or removed, new neuron types can be incorporated in the circuit, and neuronal properties can be drastically modified by changes of membrane conductance or transmitter type. A neural circuit evolves when any of these changes modifies significantly its structure and function. To reconstruct how circuits change over time, it is also important to understand the constraints that operate on their evolution. Strong functional constraints might explain the conservation of some circuits, but analogous circuits might also evolve independently as the best solutions to solve the same problem. The anatomy and function of a circuit can simply change through modifications of connections between its neurons.

11.2 The Cough Reflex

Cough reflex is a multifaceted, precisely timed, neuromuscular phenomenon characterized by the precise concurrent and sequential coordination of the activation patterns of the diaphragm, various muscle groups of the chest wall, cervical muscles, abdominal muscles, laryngeal abductor and adductor muscles, and medullary and higher cortical regions of the brain [6, 7]. Impairment or absence of the coughing mechanism can be harmful and even eventually fatal. Cough is essential protective and defensive act whose action secures the removal of mucus, noxious substances, and infections from the larynx, trachea, and larger bronchi. Abnormalities in cough can occur in any segment of the cough reflex. Abnormalities in the afferent part, such as in children with neurological disorder, lead to a predisposition to silent aspiration and subsequent chest infections. Similarly, abnormalities in the efferent part, such as in neuromuscular disorders, lead to an ineffectual cough and risk of chest infections. On the other hand, cough may be the first overt sign of disease of the airways or lungs when it represents more than a defense mechanism, and by its persistence may become a helpful pointer of potential disease for both patient and physician. Nearly all conditions affecting the respiratory system and some extrapulmonary conditions may cause cough, but the physician's main concern is ruling out the presence of more serious conditions that require prompt treatment [8].

A simplistic description of the cough reflex that is turned on or off during disease conditions, consisting of an afferent arm with cough receptors, the afferent pathway, the central processing pathway, and the efferent pathway, is imperfect. Recent research has demonstrated that peripheral triggers for coughing can involve one or more subsets of airway afferent nerves [8]. It has also been suggested that the distinct neural phenotypes of the nodose and jugular afferent nerves, exhibiting different peripheral and central projections at the brainstem and the cerebral cortex, are not evenly involved in the cough reflex [9, 10]. This novel neural aspect of the cough reflex suggests the presence of a complex network of pathways that manage the coughing process. Recent studies have also demonstrated that the afferent nerves of the cough reflex not only transport the signals induced by a stimulus but also

generate complex on-site and distal responses. Cough has three defining features: an initial deep breath, a brief powerful expiratory effort against a closed glottis, and the opening of the glottis with closure of the nasopharynx and vigorous expiration through the mouth. Within this process there are several variants. Last decade have witnessed a growing interest in basic and clinical research on cough. As a result, robust changes have emerged in our knowledge of cough neurophysiology and novel clinical etiologies [11–13]. Cough is a complex motor act, and its different components, frequency, effort (intensity), and the balance between inspiratory and expiratory components reveal various regulatory processes that are often neglected [14–16]. Cough characteristics and its acoustic features depend on the velocity of airflow, dimensions of the vocal tract and airways, and location of sound generated [17]. Cough sound is due to the vibration of larger airways and laryngeal structures during turbulent flow in expiration. Airway structure, rheological properties of the mucus, and the shearing of the secretions from the airways influence cough sound. When evaluating a child with cough it is important to establish the duration and nature of cough to determine appropriate management. In children acute cough is defined as a cough of less than 2 weeks duration. Subacute cough is cough of 2–4 weeks duration. Subsequently chronic cough is defined as greater than 4 weeks duration. This is based on evidence that show greater than 90% of upper respiratory tract infections have resolved by this time. In addition, it means children with serious illnesses, such as a retained foreign body, are evaluated promptly.

11.3 The Cough Reflex Throughout Life

Like other systems, physiological and anatomical aspects involving cough undergo maturation, and thus there are developmental aspects of cough. Maturation of the cough reflex, modifications in the structure of the respiratory tract, and immunological changes are the main factors that render why the common causes of cough in children are different to that in adults. During childhood, developmental phenomena of the respiratory components, such as modifications in the anatomy and functions of the respiratory tract, can influence the cough reflex. Changes in the structure and conformation of the upper and lower airways have also been widely investigated, and tracheobronchomalacia (TBM) has been consistently reported in children with chronic cough [18–24] (Fig. 11.1). In early infancy, this has been attributed to physiological development of the trachea [25, 26]. In subjects with tracheomalacia (TM), a marked dynamic compression of the trachea has been reported, owing to the instable tracheal wall, that may impair the efficiency of mucus clearance via coughing, thereby resulting in the characteristic brassy cough. Animal studies also report similar findings in which the growing airway stiffens due to developmental changes in the airway geometry, leading to an increase in the ratio of cartilage to soft tissue in conjunction with an increase in cartilage glycosaminoglycans that also stiffen the cartilage rings [27, 28].

The bronchi in immature animals and human infants are vulnerable to collapse by small changes in transmural pressure [29]. In normal adults, the area occupied by

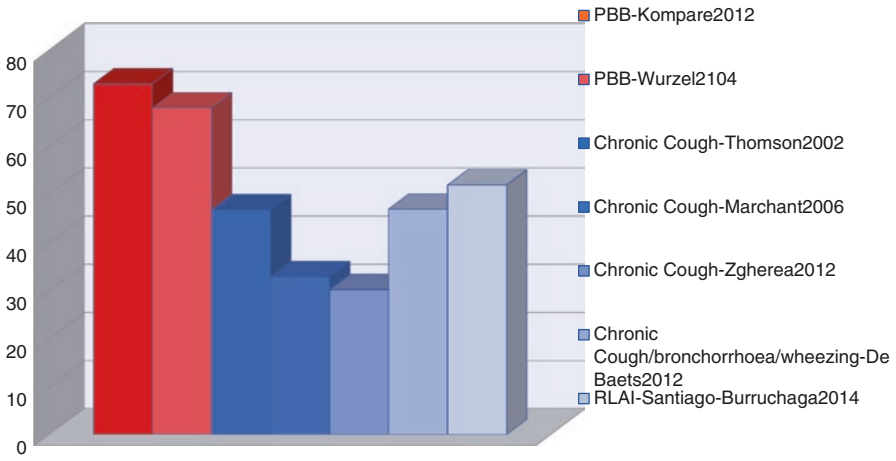

Fig. 11.1 Prevalence of malacia in children with chronic cough and protracted bacterial bronchitis [18–24]

the mucus gland constitutes of approximately 12% of the bronchial wall, while in children, the area is approximately 17% of the wall [30], leading to greater mucus secretion during childhood. This difference in composition suggests that mucus gland hypertrophy might be a more significant change in children than in adults. Numerous investigations have underlined the helpfulness of the coughing sound (dry or wet) in guiding the diagnostic approach [31]. In addition, immunological response undergoes developmental and memorial processes that make infection the overwhelming cause of cough in preschool children. Moreover, children are more vulnerable to various environmental factors [32]. The immune system is relatively immature at birth and has to evolve during a life of exposure to multiple foreign challenges through childhood, via young and mature adulthood (including pregnancy), to the decline of old age. The immune system gradually matures during infancy. Critical early protection against many infectious diseases previously experienced by the mother is given by the passive IgG antibody transferred from the mother transplacentally and in milk. Once that fades away, young children become more vulnerable to infections, though by then better armed with the maturing innate and adaptive immune systems. The risks are now much reduced by vaccinations, which stimulate protective immune responses in the maturing immune system [33]. Nevertheless, children may still acquire viral, bacterial, and parasitic infections that have to be fought off and controlled by immune responses. Besides promoting recovery, such antigen stimulation results in immunological memory [34, 35]. Thus, over time, protection provided by the immune response increases, and young adults suffer fewer infections. This accumulation of immunological memory is an evolving feature of the adaptive immune response. The memory persists into old age but then may fade.

The pediatric coughing process is characterized by an “intact” cough reflex network. A fundamental challenge in understanding this observation is the

identification of neural growth at a young stage and tracking the modifications in the following years, as brain development is a complex process. Although the most rapid phase of brain development occurs during the first few years of life, this process continues well beyond infancy [36]. A study by Lebel et al. using diffusion tensor magnetic resonance imaging (MRI) demonstrated that the brain maturation processes for white matter and deep gray matter continue, and most of the brain wiring is not fully completed until adolescence or, in some structures, until the twenties [37]. This study revealed that some brain connections mature later and at a slower rate than others. The brain structure at any point in time is the result of the interaction between genetic, epigenetic, and environmental factors, and advances in neuroimaging modalities have been helping to explore the influences of genetic and environmental factors on brain development [38].

During nervous system development, neurons extend their axons to reach their targets to form functional neural circuits [39, 40], which form the basis of neural function. Incorrect assembly, or an injury to such circuits, can result in nervous system disorders. The role of these neural developmental processes in the cough reflex circuit has yet to be defined. However, we can hypothesize that an injury during the developmental phase may produce lifelong alterations in the neural connections. In animal models with inflammation-induced hyperalgesia, the neuronal circuitry and mechanisms underlying hyperalgesia were found to be persistent beyond the neonatal inflammation period into adulthood [41].

Fair et al. used computational analyses, in combination with a developed functional MRI technique that measures spontaneous brain activity, to understand the principles that guide the maturation of the human brain [42]. They find that brain regions in children communicate with other regions more locally but that over age communication becomes more distributed. Interestingly, the efficiency of communication in children is comparable to that of the adult. Levy et al. employed magnetoencephalography (MEG) to monitor oscillatory brain responses in children, adolescents, and adults to others' pain [43]. Their findings suggested that empathy for pain develops along a gradual course from sensory alpha band enhancement, through sensory alpha band suppression coupled with beta band modulation, and culminating in viceromotor gamma band activity. Thus, a uni-rhythm alpha response in childhood gradually integrates beta in adolescence and gamma in adulthood into a multi-rhythm, excitatory-inhibitory exchange operating across brain sites implicated in sensorimotor processing, affect salience, embodiment, and interoceptive representations. This progression involves the gradual orchestration of several rhythms, distinct neural networks, and mechanisms of enhancement with those of suppression. It has been suggested that humans' protracted maturity enables the great plasticity of the human brain and its impressive capacity to adapt to multiple ecologies and integrate contextual determinants into its own functioning [44].

There is substantial evidence that microglia are important cellular players during early brain maturation, and consequently any perturbation to their physiological function, such as an infection or inflammation, during the developmental period can result in defective maturation of the synaptic circuits [45]. Both loss of physiological function and gain-of-toxicity in microglia during the developmental phase can

cause profound alterations in brain wiring. Abnormal synaptic pruning as well as reduced release of trophic factors can also induce aberrant or dysfunctional circuit formation. Additionally, the release of pro-inflammatory cytokines can directly modulate synaptic activity, thus increasing neuronal excitability [46]. The genes responsible for the production of sensory neuropeptides are enhanced in vagal sensory neurons following airway inflammation evoked by allergens or viral infections [9]. Neurotrophic factor-driven changes in gene expression within the vagal afferent nerves are reversible for a few weeks during postnatal development, but they can become persistent or irreversible later in life [47, 48]. Thus, one might hypothesize that airway inflammation and infection during early life might lead to long-lasting changes in the airways' neurobiology that may persist until adulthood. In support of this hypothesis are the recent findings by Dicpinigaitis et al., who demonstrated a nearly 12-fold higher prevalence of the Arnold nerve reflex in adults with chronic cough compared to that of controls, whereas such an increase was not observed among children with chronic cough (3%) in comparison with healthy children (2%) [49]. Interestingly, the prevalence of ACE inhibitor-induced cough in adults is reported to be in the range of 5%–35%, while in children, it is reported to be relatively sporadic. Alharbi et al. found that the prevalence of such instances increased with age until a plateau was reached at middle-adulthood (40–59 years) [50]. The incidence of cough in children receiving ACE inhibitors, as reported by Baker-Smith, was low (3.2%) and was similar to that in children receiving angiotensin receptor blockers (1.8%) [51]. In adults in up to 42% of patients, the cough remains persistent despite extensive investigations and trials of treatment; this is often referred to as chronic refractory cough (CRC) [52]. CRC is hardly described in children. Cho et al. have demonstrated that subjects with CRC were less able to voluntarily suppress capsaicin-evoked cough compared to healthy controls [53]. This suggests brain failure to control the cough reflex in subjects with CRC.

11.4 Cough in Children

Chronic cough in children is known to be different from that in adults in terms of common etiologies and management [54, 55]. However, in the last decade, research has led to a reconsideration of the etiology of chronic cough in children (Table 11.1). The underlying causes of chronic cough in children may predominantly include postinfectious cough, protracted bacterial bronchitis (PBB), airway malacia, and bronchiectasis, in addition to the universally common etiologies, such as asthma. However, by adolescence, the causes of cough are more likely to become those common in adults, namely, gastroesophageal reflux, asthma, and upper airway syndrome. Currently, attention has focused on PBB as the major cause of chronic cough in preschool-aged children and as a possible precursor of bronchiectasis. PBB is not a new entity, and PBB-like conditions were being reported during the last century [56]. In 2006, Marchant et al. made a breakthrough in our knowledge about the etiology of chronic cough in children [21]. An ERS task force has recently developed a reliable PBB definition for day-to-day clinical practice in which all three of

Table 11.1 Phenotypes chronic cough in children

Postinfectious (spontaneous resolution)
Airway persistent infection (PBB, bronchiectasis)
Airway anomaly (Malacia)
Airway inflammation (eosinophilic or neutrophilic)
Airway aspiration (RGE, foreign body)
Upper airway syndrome (rhinosinus diseases)
TIC and somatic syndrome
Drug-induced (ACE-inhibitors)
Extra-pulmonary
Specific disease
Cough reflex hypersensitivity without an identified cause (rare in children)

Table 11.2 Symptoms and signs to rule out and tests to perform before clinical diagnosis of PBB [57]

A. Symptoms and signs to exclude before clinical diagnosis of PBB	
Symptoms	Chest pain, history suggestive of inhaled foreign body, dyspnea, exertional dyspnea, hemoptysis, failure to thrive, feeding difficulties (including choking/vomiting), cardiac or neurodevelopmental abnormalities, recurrent sino-pulmonary infections, immunodeficiency, epidemiological risk factors for exposure to tuberculosis
Signs	Respiratory distress, digital clubbing, chest wall deformity, auscultatory crackles
Tests	Chest radiographic changes (other than perihilar changes), lung function abnormalities

the following criteria should be fulfilled: (a) presence of chronic (>4 weeks duration) wet or productive cough; (b) absence of symptoms or signs (i.e., specific cough pointers) suggestive of other causes of wet or productive cough (Table 11.2); and (c) resolution of cough following a 2–4-week course of an appropriate oral antibiotic [57]. Awareness about PBB as the cause of chronic cough in children is currently increasing, as supported by the clinical observations showing that its recurrence is a potential precursor of chronic suppurative lung disease or bronchiectasis. Wurzel et al., in a long-term prospective follow-up study, described a subgroup of children with recurrent PBB who were subsequently diagnosed with bronchiectasis [58]. Clinical conditions of a single episode of PBB, extended PBB that needs prolonged therapy, or recurrent PPB imply the presence of distinct endotypes of this disease that are yet to be defined [59].

The clinical pictures of PBB, CSLD, and bronchiectasis are overlapping entities, but from a pathophysiological point of view, it might well be that these conditions are part of a spectrum of symptoms reflecting disease progression [60]. King et al. investigated 182 subjects with bronchiectasis and distinguished two phenotypes of patients with bronchiectasis who had developed a chronic productive cough in childhood (before 16 years of age) compared with those who had developed a productive cough as adults [61]. In the childhood-onset group, 24% of the subjects had

a potentially causative factor identified, such as being postinfectious, an IgG subclass deficiency, ABPA, PCD, and Young's. The clinical features of the childhood onset and adult onset groups differed in several factors. The median duration of the productive cough was tenfold longer in the childhood-onset group ($p < 0.001$). The volume of the daily sputum production was also higher in the childhood-onset group, but this did not achieve statistical significance. The prevalence of hemoptysis showed a trend to be higher in the childhood-onset group, possibly reflecting increased airway inflammation. The incidence of rhinosinusitis was almost threefold higher in the childhood group. The childhood-onset group had more than three times the prevalence of crepitation, possibly reflecting the increased sputum production. Moreover, the authors observed that there was also a bimodal distribution of age onset with the onset of a productive cough most common in the first 15 years of life followed by the onset of a productive cough in subjects over the age of 50. There were relatively few subjects who developed the onset of a productive cough between the ages of 16 and 50 years. These findings suggest that immune function is best during this time lapse and then declines [62]. More interestingly, Field reported that as children became adults, their symptoms improved regardless of the treatment [63]. Although once considered rare, there is a global resurgence in bronchiectasis. Despite its increasing prevalence over the last 15 years and its substantial impact on morbidity and mortality, bronchiectasis remains relatively underrecognized in the general community [64]. The diagnosis of bronchiectasis is highly dependent on case-ascertainment and hence its awareness is important. Although considered to be of a non-reversible nature, mild bronchiectasis determined by radiography might be reversible at any age if treated early, and the lung function decline associated with disease progression could then be halted. Although some management strategies are extrapolated from cystic fibrosis or adult-based studies, or both, non-cystic fibrosis pediatric-specific data to help diagnose and manage these children still need to be generated [65]. A myriad of heterogenous risk and/or etiological factors may lead to bronchiectasis in children. These factors and the various clinical symptoms vary among settings and countries, but share the common thread of cycles of chronic cough, recurrent respiratory infections, and endobronchial suppuration with persistent infection and inflammation. Interrupting these processes as early as possible is necessary to reverse and/or halt disease progression and further tissue damage. This requires early diagnosis that is dependent on clinical awareness and use of pediatric-specific rather than adult-derived definitions and data. Chang et al. have recently proposed a definition of bronchiectasis as a clinical syndrome (persistent or recurrent (>3) episodes of chronic (>4-weeks) wet or productive cough, sometimes with coarse crackles and digital clubbing), confirmed radiographically using pediatric BAR data (abnormal when >0.8). If sought, neutrophilic endobronchial suppuration is present. Using pediatric-specific rather than the adult-derived definition (i.e., irreversibility and a single higher BAR value) is important in the context of stimulating efforts to prevent disease progression or even reverse the changes with early and intensive treatment in children [66].

TM is a condition of excessive tracheal collapsibility, due either to disproportionate laxity of the posterior wall (*pars membranacea*) or compromised cartilage integrity. As a result, the anterior and posterior walls appose, reducing the tracheal

lumen opening and creating a shape abnormality during bronchoscopy. TM may be localized or generalized. If the main bronchi are also affected, the condition is called TBM. TM and TBM may be primary abnormalities of the large airways or associated with a wide variety of congenital and acquired conditions. The evidence on diagnosis, classification, and management is scant. There is no universally accepted classification of severity. Clinical presentation includes early-onset stridor or fixed wheeze, recurrent infections, brassy cough, and even near-death attacks, depending on the site and severity of the lesion. Diagnosis is usually made by flexible bronchoscopy in a free-breathing child but may also be shown by other dynamic imaging techniques. Management may be medical or surgical, depending on the nature and severity of the lesions, but the evidence base for any therapy is limited [67]. This diagnosis should be considered in children who have persistent or protracted recurrent airway symptoms (persistent or recurrent "wet" cough, unusual cough, expiratory stridor, wheeze, rattling or rattly respiration, dyspnea/respiratory distress), recurrent PBB, pneumonia (particularly with atypical radiographic features such as persistent o recurrent collapse), localized gas trapping, and unusual radiographic densities [68]. Suspicion of this diagnosis should also be increased in children who have syndromes involving cardiac disorders, tracheoesophageal fistula, bronchopulmonary dysplasia, persistent wheezing including "happy wheezers," and all those who have undergone prolonged intubation or tracheotomy [69].

Children who have had a respiratory illness can be left with a chronic dry cough. These children do not have any specific cough pointers and will resolve over time without treatment. Management involves reassurance and reassessment to ensure no specific pointers develop. Initially, postinfectious chronic cough was attributed to the extensive disruption of epithelial integrity and airway-induced inflammatory responses in the upper and/or lower airways, which were suspected to expose sensory nerve endings in the airway lining to prolonged and excessive stimulation [70]. However, recent experimental studies have demonstrated that postinfectious cough is a complex process that involves cough receptors in the afferent nerves and peripheral and central neural circuits involved in the cough reflex [71, 72]. Postinfectious cough is self-limited, usually resolves in time, and appears to be the tail end of an infection. Pertussis infection remains the most common cause of postinfectious chronic cough. Cough may persist for months after acute infection. In many respiratory infections, cough is often the last symptom to disappear. Children aged 2–5 may have 4–10 episodes of respiratory infection, especially if they attend day care. Persistent coughing after each bout may thus blend seamlessly into the next infection and this may be reported erroneously as chronic cough. A careful history and inquiry on the timing of coughing bouts are helpful in differential diagnosis. Observation of cough waning after the child's withdrawal from day care confirms the diagnosis.

11.5 Conclusion

Chronic cough in children may be representative of a simple, spontaneously resolving cough or a specific, serious disorder. Children with chronic cough should be evaluated carefully using protocols specific to children. Pediatric guidelines and

clinical algorithms have identified pointers or "red flags" to consider during investigations. A correct interpretation of the phenotypic presentation can be translated into guidance for workup in primary care. Performing a thorough history and physical examination is crucial to starting an individualized workup. Although the concept of individualized diagnosis and treatment of chronic cough is attractive, it is highly debated how to pursue it in a clinical setting. For this purpose, a thorough clinical profile describing the child may be helpful in identifying management strategies. A correct interpretation of the phenotypic presentation can be translated into guidance for workup. Regardless of the setting and age, children with chronic cough should be evaluated carefully using protocols specific to children. Knowledge of the pathophysiology of the various conditions that cause chronic cough is vital to its correct diagnosis and management. The use of cough management protocols or algorithms improves clinical outcomes, and cough preventative strategies for chronic cough in children include reduced exposure to infectious agents, the use of adequate antibiotics, immunization, and easy access to health systems. Care of children with chronic cough should be conducted by skilled pediatric centers. Future clinical and research challenges include understanding the various processes of chronic cough and improving its management in childhood.

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Part III

Cough Therapy

Pharmacological Therapy of Acute and Chronic Cough

12

A. Zanasi, M. Mazzolini, and U. Caliceti

12.1 Introduction

A first consideration when approaching the treatment of cough should be the possibility to treat its underlying cause. Several algorithms were developed over time and proved to be effective [1, 2]. However, in those cases of chronic cough where a reliable diagnosis cannot be made or a specific treatment fails, an empiric or symptomatic approach is frequently attempted. In the settings of acute cough, symptomatic treatment is often the first line of therapy. To date, there are countless preparations, mainly available as over-the-counter products, for the symptomatic control of cough. They also include central and peripheral antitussives, mucolytics and some antihistamines. As discussed below, the effectiveness of such drugs in cough control remains controversial [3]. For the sake of completeness, this chapter also discusses some other drugs often used to treat cough, though some of them are not commonly classified as antitussive agents.

In recent years, the concept of cough hypersensitivity syndrome (CHS) [4] was developed, according to which persistent cough should be regarded as the consequence of hypersensitization of the central and/or peripheral mechanisms leading the physiological cough reflex. Accordingly, the treatment paradigm has shifted towards neuromodulation.

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12.2 Drugs in Current Use for the Treatment of Cough

12.2.1 Cough Suppressants

The most common approach to the non-specific therapy of cough is the inhibition of the cough reflex. Several mechanical stimuli trigger the sensory receptors and modify their discharge. The excitability of the sensory receptors can be targeted by drugs, as in the case of peripheral antitussives. On the other hand, drugs acting on the brainstem sensory afferents that produce cough are usually considered central antitussives. The inhibition of the cough reflex, especially in the central nervous system, can present serious adverse effects.

12.2.1.1 Codeine

Codeine, or 3-methylmorphine, is an alkaloid contained in opium but it is mainly obtained via a semi-synthetic process of morphine methylation. Codeine inhibits cough not only by a suppressing action in the brainstem but also acting on peripheral receptors [5, 6]. Codeine is probably the most renowned antitussive agent due to its widespread use, but may also present serious side effects [7, 8]. Irrespective of its use and abuse, randomized controlled trials of codeine in upper respiratory tract infections (URTIs) have not shown greater efficacy than placebo [9, 10]. In patients with chronic bronchitis a few studies contain recommendations for the use of codeine to obtain short-term relief [11–14]. Dihydrocodeine was also tested in cough associated with lung cancer with favourable results and acceptable side effects [15]. Codeine is not recommended in children younger than 12 years old due to the lack of efficacy and the side effects [16].

12.2.1.2 Dextromethorphan

Dextromethorphan is a widely used non-opioid antitussive agent. Dextromethorphan is considered a central antitussive and increases the threshold for coughing of the cough reflex, without inhibiting ciliary activity. The quality of the studies on dextromethorphan is generally low, most are outdated and include several conditions in the study population. Despite these limitations, dextromethorphan was found to decrease cough severity with comparable results to codeine [17]. In a small study comparing the antitussive effects of 30 mg codeine and 60 mg dextromethorphan, both were superior to a lower dose of dextromethorphan (30 mg) and placebo, but significant differences were found between 30 mg codeine and 60 mg dextromethorphan [14]. Similar results were reported in another double-blind randomized study with 20 mg dextromethorphan and codeine, with a slight superiority of dextromethorphan [18] and potentially a more favourable safety profile.

12.2.1.3 Levodropropizine

Levodropropizine activates C-fibre sensory afferents which cause the inhibition of cough and is thus generally considered a peripherally acting antitussive [19]. The efficacy of levodropropizine was investigated in several settings ranging from acute

cough to advanced lung cancer [20]. Two randomized controlled trials in adults [21, 22] with bronchitis and non-productive cough showed favourable results in symptom relief, and this was also found in three randomized controlled trials (RCTs) in children [23–25].

In the above study of codeine [15], levodropropizine was also effective in cases of cough due to advanced lung cancer. The treatment was well tolerated in both adults and children without significant side effects [19]. Despite the overall favourable results, the endpoints are too heterogeneous to draw any final conclusions on levodropropizine recommendations.

12.2.2 Mucoactive Drugs

Drugs included in this category act by modifying the rheological features of mucus. The main observed effects are:

(a) Mucolytic: reducing mucus viscosity to ease clearance
(b) Expectorant: increasing mucus secretion
(c) Mucoregulatory: normalizing mucus features

The available compounds can present one or more of the above properties; however the observed in vitro effects do not always correlate to a reduction in cough symptoms.

12.2.2.1 N-Acetylcysteine (NAC)

Probably the most renowned drug in this category, NAC dissociates mucin disulphide bonds to reduce mucus viscosity. Several papers suggest that NAC exhibits not only mucolytic properties but also antioxidant and anti-inflammatory effects [26–28].

NAC is currently mainly prescribed for chronic bronchitis and chronic obstructive pulmonary disease (COPD) where it shows favourable results, although the efficacy of lower doses is still controversial [29, 30]. There are only a few studies on NAC including patients presenting cough without significant respiratory comorbidities. In the Cochrane review on children with acute cough due to URTIs, NAC seems to show potential benefits on cough among these paediatric patients [31]. Results need to be interpreted with caution because most of the studies were conducted with poor standardization of populations, concurrent medications and outcome measures; NAC appears to be safe in children older than 2 years [29–31].

In a randomized trial in adults without chronic respiratory comorbidities receiving NAC 600 mg twice daily for 6 months [32], results showed a significant reduction of cough in the treated arm, but specific tools for cough assessment were not used. NAC shows valuable antioxidant, anti-inflammatory and mucolytic properties, but there is lack of evidence supporting its use as symptomatic therapy in patients with cough without chronic bronchitis or COPD.

12.2.2.2 Erdosteine

Erdosteine has antioxidant and mucolytic properties [33, 34]. In vitro, erdosteine also enhances the ciliary beating frequency and reduces bacterial adhesiveness [35, 36]. It was mainly studied in COPD patient showing favourable results in a small randomized controlled trial. Patients treated with erdosteine had less exacerbations, reduced hospital stay and improved quality of life (QoL) compared with placebo [37]. Similar results were observed among COPD patients with acute exacerbations. Indeed, patients who received erdosteine had better outcomes during hospitalization [38]. Erdosteine appears to be effective in chronic bronchitis as additional treatment. There are no standardized studies focusing primarily on cough and therefore its antitussive effectiveness cannot be assessed.

12.2.2.3 S-Carboxymethylcysteine (SCMC)

S-Carboxymethylcysteine has mucoregulatory, antioxidant and anti-inflammatory properties [39–41]. SCMC is thought to perform its mucoregulatory action by increasing both the synthesis of sialomucins—regulating the balance between sialomucins and fucomucins [42]—and chloride transport across the airway epithelium [43]. Infections and inflammation alter the original viscoelastic properties of mucus and their normalization induced by SCMC could favour more effective airways clearance [44]. Due to its properties, SCMC was mainly studied in patients with COPD and chronic bronchitis. Meta-analyses and reviews have reported potential benefits on symptoms, QoL and exacerbations [45, 46]. In the absence of targeted studies on cough, in otherwise healthy subjects, it is not possible to recommend SCMC as a valuable symptomatic treatment. In the paediatric population, only one study was considered in the Cochrane meta-analysis [31]. However, it includes mostly infants and its results are not applicable to older children [47].

12.2.2.4 Bromhexine (BHC)

Bromhexine is a derivative of vasicinone, a natural compound isolated from leaves of *Adhatoda vasica*. Studies in animals and humans showed that BHC acts as a mucoregulatory agent by increasing phospholipid concentration in airways, emptying mucous glands and enhancing ciliary transport [48]. The literature on BHC is wide but most of the studies were conducted before the 1990s and do not include standardized endpoints (i.e. QoL validated scores). As for larger trials, Valenti et al. conducted a randomized controlled trial (RCT) in 237 patients with COPD showing greater improvements in symptoms and respiratory functional tests [47]. Two trials also evaluate the effectiveness of BHC both in lower and upper respiratory tract infections. Cough was assessed by means of the visual analogue scale or the nominal score and patients treated with BHC showed a significant reduction in symptoms [49, 50]. Similar results were observed in children [48]. The available literature consists mainly of outdated studies and the results are difficult to compare, although they are often associated with favourable outcomes.

12.2.2.5 Ambroxol

Ambroxol is the active metabolite of bromhexine; it enhances mucus and airways clearance by increasing secretion and lung surfactant production as well as by stimulating mucociliary activity [51, 52]. Moreover, ambroxol exhibits anti-inflammatory, antioxidant properties and in vitro anti-viral and anti-bacterial activity [53–57]. There are several studies on obstructive lung disease and chronic bronchitis. Results on the prevention of exacerbations are conflicting [58, 59] but, overall, a favourable outcome in symptoms was observed [58–61]. In a four-arm comparison RCT with cefuroxime, myrtol and placebo, ambroxol led to better recovery in patients with acute bronchitis compared to placebo, but had comparable efficacy to the other active treatments that were investigated [62]. In a recent real-life survey, the satisfaction of pharmacy customers with ambroxol preparations was assessed. The study showed an overall improvement in symptoms (especially cough), but no statistical analysis was conducted. Moreover, there were no clinical evaluations so that the results are not comparable to clinical trials [63]. As is the case for other products above, ambroxol shows a wide range of interesting properties but the lack of consistent data in the literature prevents one from making any specific recommendations.

12.2.2.6 Hypertonic Solutions (HSs)

Hypertonic solutions administered by aerosol increase mucociliary clearance through several mechanisms. HSs increase the water transport inside the airways due to higher osmolarity [64] and reduce the viscosity of secretions by both separating DNA from mucin in the infected mucus and disrupting ionic bonds [65, 66]. HSs are mostly used to increase expectoration in hypersecretory conditions and to obtain mucus samples [66]. Studies on cystic fibrosis (CF) showed increased expectoration and reduction of exacerbations with regular use [67]. Among patients with non-CF bronchiectasis inhaled mannitol was shown to be beneficial, although results with hypertonic saline are more controversial [68].

12.2.2.7 Guaifenesin (Glyceryl Guaiacolate, GG)

Guaifenesin shows an expectorant activity by stimulating the gastro-pulmonary reflex and increasing the hydration of the airway mucus [69]. GG might also reduce cough sensitivity in patients with acute URTIs [70, 71]. Despite several potential mechanisms of action, the results of the studies on URTIs and acute bronchitis are controversial [72–75]. The evidence available in chronic bronchitis is outdated and inconsistent [73, 76, 77] to support current indications.

12.2.3 Other Drugs Having an Effect on Cough

12.2.3.1 Antihistamines

The role of antihistamines is limited to cough due to a common cold. The therapeutic effect is secondary to the cholinergic blockade induced only by the systemic administration of sedating antihistamines. This mechanism, especially in

combination with alpha-adrenoceptor agonists, is likely to reduce the amount of secretions in the nasal airways [78]. Overall though, the evidence for certain older H_1-receptor antagonists having an antitussive effect seems to be unrelated to H_1-receptor antagonism. Results from the studies are controversial [79–82] and evidence is too weak to support a strong recommendation [3]. The sedating effect of older antihistamines may lead to an unfavourable risk/benefit ratio. The ACCP guidelines recommend the combination of a first-generation H_1-antihistamine and a decongestant as the treatment of choice for adult's chronic cough due to upper airway cough syndrome (formerly known as postnasal drip syndrome) and acute cough due to a common cold. Studies examining the mechanism by which certain H_1-antihistamines exert an antitussive effect, as well as proper trials demonstrating clinical efficacy, are still needed.

12.2.3.2 Local Anaesthetics

Antitussive effects of local anaesthetics have been reported in the literature and they seem to be related to the involvement of the sensory nerves in the cough reflex. Local anaesthetics can inhibit both experimentally induced cough and cough in a variety of clinical circumstances. The antitussive activity is presumably due to the ability of local anaesthetics to block Na_V channels in the sensory nerves [83]. There is mostly information concerning the use of lignocaine/lidocaine. For example, inhaled lignocaine (20 mg) was shown to suppress cough induced by inhaled capsaicin in non-smoking volunteers [84]. It was suggested that different types of local anaesthetics affect different airway reflexes in various ways, even when administered at doses producing the same degree of oropharyngeal anaesthesia [85].

12.2.3.3 Bronchodilators

Studies in both experimental animals and humans indicate that airway calibre increases the sensitivity of the afferents involved in the cough reflex though it was difficult to demonstrate this effect. Therefore, bronchodilators might have a role—although rather minor—in the treatment of cough. However, even if bronchodilators represent the standard of care in the treatment of airway obstruction associated with asthma or COPD, controversy persists regarding the mechanism(s) by which these agents alleviate cough. Furthermore, the available evidence indicates that the effects of bronchodilators on cough are rather inconsistent in humans and casts doubt on the appropriateness of the common practice of using bronchodilators in the treatment of patients with cough without any other evidence of airway obstruction [86].

12.2.3.4 Corticosteroids

Corticosteroids are widely used in the treatment of airway disease and corticosteroid responsive cough syndromes. Most evidence for efficacy has been obtained in asthmatic and non-asthmatic eosinophilic bronchitis (NAEB). Inhaled corticosteroids (ICS) seem to be effective in asthmatic patients presenting cough. The anti-inflammatory effects of ICS in reducing post-viral cough have also been studied [87]. A significantly faster and greater decline in cough frequency was reported with extra-fine hydrofluoroalkane-beclomethasone dipropionate (HFA-BDP) compared

with placebo in patients with cough lasting more than 3 days but less than 2 weeks. The Cochrane Database of Systematic Reviews concluded that any clinical impact with very high dose ICS is unlikely to be beneficial [88].

12.2.3.5 Muscarinic Receptor Antagonists

Several research works have demonstrated an antitussive effect of muscarinic receptor antagonists in animals' studies [89–92]. Ipratropium showed controversial results in human studies. In two studies, ipratropium inhibited cough induced by nebulized distilled water and hypotonic saline solution in healthy volunteers [93] as well as in subjects with asthma [94]. However, four other studies were unable to confirm the antitussive effect in healthy volunteers; ipratropium bromide was unable to inhibit cough due to capsaicin [95] as well as cough due to capsaicin, prostaglandin $F_{2\alpha}$, and their combination [96]. Tiotropium, another commonly used long-acting antimuscarinic agent, was found to have potential antitussive effects. In patients with acute viral upper respiratory infections, tiotropium inhibits cough reflex sensitivity to capsaicin, while in uncontrolled asthmatic patients already receiving inhaled corticosteroids and long-acting β-agonists, it reduces cough severity and capsaicin sensitivity [97, 98]. The mechanisms of cough inhibition by antimuscarinic agents is still unclear. Bronchodilation was not associated with reduced cough sensitivity in the studies [97, 98]. Vagal activity downregulation may contribute, apart from inducing bronchodilation, reducing airways mucus, local blood flow and inflammation, resulting in lowered cough receptor sensitivity [99]. Despite the overall favourable findings, the role of antimuscarinic agents in cough is still debated.

12.2.3.6 Natural Remedies and Alternative Medicine

Recently, the use of complementary medicine is increasing and, among the most frequent conditions, respiratory complaints are often approached with homoeopathic remedies [100, 101]. Several studies were conducted in acute cough and some beneficial effects have emerged from the results [50, 102–105]. More than in previous categories, the patient's belief and the "placebo effect" are frequently advocated as the most relevant bias, although the same results were observed in placebo-controlled trials. There is still a lack of standardization in study methods and the mechanism of action is not yet known. Treatments were overall well tolerated.

12.2.3.7 Honey

Honey is probably the most used "home remedy" for cough in children. Its widespread availability together with the sweet taste may be part of the reason. The mechanism of action is not fully known but antioxidant properties were reported [106]. Additionally, it has been postulated that the sweet taste may favourably influence the cough reflex [107]. Several studies have reported favourable results also when compared to over-the-counter (OTC) products and even antitussives (dextromethorphan) [108, 109]. The Cochrane review concluded that is not possible to draw any final conclusions for or against using honey. However, good tolerance and lack of significant side effects support its use in children, who would otherwise receive no treatment because of the age restrictions of several OTC products [110].

12.3 New Approaches to Treating Cough

Despite attempts at rational therapy, chronic cough can often be resistant to treatment (20–40% of cases). A necessary reinterpretation of the symptom has led to defining chronic cough as a *hypersensitivity syndrome of the receptors* distributed throughout the respiratory system. Several treatments have been developed over the past decade. These include speech pathology interventions using techniques adapted from the treatment of hyperfunctional voice disorders, as well as the use of centrally acting neuromodulators such as gabapentin and pregabalin. Potential new treatments under development are also quite promising.

12.3.1 Speech Therapy and Behavioural Treatment

This term refers to treatments aimed at the voluntary mechanism of cough reflex, which, as mentioned above, is represented by an irritation of the receptors (up-regulation), which is partially self-maintained by erroneous defensive measures and the patient's unfavourable lifestyle. This assessment and subsequent treatment are the domain of specialists in the upper airways, in particular the pharynx and larynx. Therefore, besides the otorhinolaryngologist, the speech pathologist and speech therapist are also involved.

The starting point for the speech therapist should be to identify the patient's pathophysiological and behavioural patterns on which to start a bespoke behavioural programme. It is fundamental to identify any triggers and ensure that patients learn to recognize the urge to cough and attempt to overcome it by appropriate means. Thus, the patient will also have to learn how to suppress the cough itself. When this is combined with dysphonia caused by laryngeal dysfunction, the patient should undergo phoniatric assessment to highlight any lack of coordination between breathing and phonation, or speech habits that might bring on the irritation. Laryngeal dysfunction is represented by paradoxical vocal fold motion, and one of the most typical of these is forced inspiration with the glottis closed which typically triggers coughing. Therefore, the aim of the speech therapist and behavioural therapy is to improve voluntary control over coughing, by teaching the patient to recognize the conditions that trigger the reflex and try to replace the cough with a competing action, such as breathing slowly and deeply, possibly with the mouth closed [111–115].

The group of experts mainly dedicated to this type of therapy is currently led by Anne Vertigan and Peter Gibson. In 2009, they proposed a standardized treatment based on a protocol involving four different components: (1) education; (2) cough suppression strategies; (3) vocal hygiene training; and (4) psychoeducational counselling [116].

- Component 1 is aimed at informing patients about the fact that the nature of their cough is not defensive but irritative, thus stimulating their need to try to control their symptom.

- Component 2 is aimed at making patients recognize the initial urge to cough to give them time to activate virtuous competing actions that can prevent the onset of coughing bouts. These competing actions mainly consist of trying not to open the mouth but trying to breathe slowly through the nose and relaxing the larynx and ultimately stopping breathing for a moment (voluntary apnoea). At the same time, it is useful to combine these attempts with an act of slowly swallowing saliva (or a little sip of water) with the aim of moistening the mucosa which, when dry, can become irritated, especially during speech.
- Component 3 concerns performing correct vocal hygiene which above all involves hydration of the pharyngo-laryngeal mucosa, both locally (inhalation of vapour) and systemically (drinking sufficient liquids), and highlights the importance of avoiding unfavourable behaviour patterns such as open-mouth breathing, smoking, and drinking alcohol and caffeine, because they produce a dehydrating effect.
- Component 4 is connected to the first and involves encouraging patients to accept and adopt the suggested treatment (compliance) by insisting on their potential ability to control partially their symptoms.

However, it should be underlined that although behavioural re-education treatments were introduced at the end of the 1980s [117], they have been poorly adopted. A review of the literature by Chamberlain et al. in 2013 showed that only five papers dealt specifically with this subject and only one of them was a randomized clinical study. The conclusions of these publications recognize the real usefulness of a non-pharmacological treatment to suppress or markedly reduce the symptom in most patients [118].

In the 2016 CHEST Guideline on RCC, the experts suggest that speech therapy with a multimodal approach (according to Vertigan) is a treatment to be considered when all organic causes of cough have been ruled out and after the failure of pharmacological treatment. Level 2 evidence with grade C recommendation [119].

However, in the following years some other papers demonstrated the usefulness of non-pharmacological behavioural treatment (speech therapy), which also has the added advantage of not producing side effects [120, 121].

Despite being aware of how difficult it is to apply the above protocol rigorously, we still believe it is useful to offer the patient a list of rules that can help identify remedies and attitudes that are potentially effective at reducing or suppressing the cough reflex.

12.3.2 Useful Rules for Patients

1. Always wet the vocal cords before and after prolonged use of the voice:
   - Drink a lot
   - Breathe through the nose through a moist gauze (to be avoided in asthma patients)
2. Don’t shout

3. Speak slowly
4. Take a breath frequently during speech
5. Use vocal aids for speech therapists
6. Inhibit the cough reflex as far as possible by alternative strategies (reinforced swallowing with the head flexed, little sips of water, minimal apnoea, and gauged slowed voluntary expiration)
7. Avoid scraping the back of your throat
8. Be aware of cough-triggering elements, so that you can avoid them
9. Follow food hygiene rules
10. Avoid poorly humidified settings where irritants are present

12.3.3 Neuromodulators

Pharmacological research has recently focused on central neuromodulators which act by increasing the neuronal sensitivity involved in the pathogenesis of chronic cough. They are very effective drugs and have a marked impact on improving the patients' quality of life, but potentially cause marked side effects. Furthermore, their therapeutic effect seems to wane when treatment is withdrawn.

The only neuromodulators that have been studied in double-blind randomized controlled trials to test their therapeutic efficacy in chronic cough are morphine, amitriptyline, and gabapentin [122–124]. In all three studies the drugs were effective in significantly improving the patients' quality of life. There are also studies on the efficacy of baclofen, but randomized studies are lacking [125, 126].

The available papers show how the use of these drugs greatly improves patients' quality of life. The results are promising, but at the same time their adverse effects are important [127].

The 2016 **CHEST Guideline** on the treatment of refractory chronic cough (RCC) concludes that the only neuromodulator with scientific evidence of efficacy is gabapentin. The patient must be informed, however, about side effects and possible recurrence upon withdrawal of the drug. It is **level 2** evidence and grade c randomization [128]. In recent years, transient receptor potential channels (TRPs) were considered to play a role in the development of chronic cough. TRPs are receptors expressed in C-fibre neurons involved in the cough reflex and their stimulation may lead to inflammation and neuroinflammation [129]. pH alterations, inflammatory mediators, mechanical and irritant insults as well as temperature may activate TRPs [130–132], suggesting they could be involved in the pathogenesis of cough sustained by asthma, gastroesophageal reflux and infections.

12.3.3.1 Amitriptyline and Gabapentin

Neuromodulatory agents are thought to reduce the neural sensitization found in unexplained chronic cough. In a review by Cohen et al., the overall results in unexplained cough were positive, showing a reduction in symptoms and better QoL [133]. A prospective, randomized, controlled open trial in patients with suspected post-viral vagal neuropathy, comparing the efficacy of amitriptyline versus codeine/

guaifenesin in chronic cough, showed an improvement >50% of outcome measures in a greater proportion (13/15 vs. 1/13) of subjects treated with neuromodulators compared to antitussives [134]. In a double-blind randomized placebo-controlled trial in patients with refractory chronic cough, gabapentin showed significant improvement in the Leicester Cough Questionnaire (LCQ), cough severity and frequency compared to placebo. Interestingly, no effects on capsaicin cough reflex sensitivity were observed [135]. Amitriptyline was overall well tolerated in the studies, while patients treated with gabapentin frequently reported confusion, dizziness, dry mouth and fatigue. Despite the limited literature, neuromodulators were effective in improving chronic cough. The lack of effect on cough reflex sensitivity showed by gabapentin could suggest that amitriptyline and gabapentin may also have actions outside the central nervous system.

12.3.4 Combination of Neuromodulators and Behavioural Therapy

Another recent therapeutic approach is the combination of behavioural therapy and the neuromodulator pregabalin (300 mg/day). A noteworthy randomized controlled study was performed in 2016 by Vertigan et al. on a group of 40 patients. The authors claimed that the combination of both treatments, by acting on different aspects of the cough pathway, led to complete resolution of the symptom [119].

Speech therapy reduces the cough but does not eliminate it, whereas neuromodulators are effective but have adverse effects. It is precisely for that reason that both therapies together can provide better results, even when the drug is withdrawn.

12.4 Conclusions

The treatment of chronic cough needs to be directed to the specific aetiology, rather than treating symptomatically: following current guidelines it is possible to obtain a complete or partial response, but in many patients cough remains refractive to both disease-specific therapies and current cough-suppressing medicines, creating a need for improved antitussive therapies. The new concepts of peripheral and central neural hypersensitivity and neurophenotypes allowed important advances in the comprehension of physio-pathological mechanisms involved in refractory chronic. Based on these results, new drugs have been developed, whose clinical impact has to be further analysed.

Symptomatic relief must be considered when the cough interferes with the patient's daily activities; expectorants/antitussives are used for effective symptomatic relief of productive or dry-cough. Unfortunately, much of the OTC therapy currently recommended throughout Europe is based on custom and practice and is not supported by clinical studies of sufficient quality to meet the standards of modern evidence-based medicine.

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Emerging Drugs for Chronic Cough

13

Federico Lavorini, Guja Bernacchi, and Alessio Fabbrizzi

13.1 Introduction

Cough is the most commonly reported symptom during primary care consultations and chronic cough is the most common reason for patients seeking specialist respiratory assessment. Traditionally, chronic cough has been suggested to be due to three conditions: asthma, upper airway cough syndrome and gastro-oesophageal reflux disease [1]. In most patients with chronic cough, an aetiologic diagnosis can be determined and cough can resolve after treatment. However, in some patients with chronic cough an aetiologic diagnosis cannot be confirmed after a comprehensive investigation and therapy aimed at known causes [1]. This type of cough is called unexplained ("idiopathic") chronic cough or chronic refractory cough [1]. A recent systematic review conducted by the ACCP, which included an analysis of 11 international studies of chronic cough, suggested that overall, 3–46% of patients with chronic cough have a cough that is refractory to treatment of any underlying conditions or that is unexplained [2]. Patients with refractory or unexplained chronic cough are therefore potential candidates for specific antitussive therapy. The recognition that chronic cough is characterised by hypersensitivity of the peripheral and central neural pathways involved in cough has expanded the range of potential therapeutic targets currently under evaluation [3]. Although there are currently no treatments approved by the Food and Drug Administration or European Medicines Agency for treatment refractory or unexplained chronic cough, some interventions targeting neuronal hyperresponsiveness have been shown to be effective in randomised, placebo-controlled trials.

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This chapter will provide an update on emerging antitussive drugs focusing on their putative site of action (central or peripheral) and preclinical and clinical findings to date.

13.2 Treatments with a Central Site of Action

Sensory input from the upper and lower airways to the brainstem is relayed to higher brain regions where they modulate the varying sensory and motor responses that accompany coughing. Chronic cough patients appear to have altered brain activity with evidence of both central sensitisation and dysfunctional inhibitory control [4]. A greater understanding of this disordered central processing is required and more selective targeting of pathways will be key to improved therapeutic control of troublesome coughing.

13.2.1 Opiates

The notion that opiates are an effective cough suppressant has arisen from old animal studies [5]. The only randomised controlled study of opiates conducted in patients with chronic intractable cough was undertaken by Morice and colleagues which showed that 5 mg of morphine sulphate twice daily for 2 months was an effective antitussive [6]. More recently, the antitussive properties of tramadol, an opioid medication with a similar structure to codeine and morphine, have been investigated in a pilot study and shown to be effective [7]. A detailed description of these compounds used for treatment of cough is available elsewhere in this book.

13.2.2 GABA-Related Compounds (Gabapentin, Pregabalin)

Gabapentin and pregabalin are centrally acting neuromodulators primarily used for the treatment of neuropathic pain and epilepsy [8, 9]. Both are structurally related to the inhibitory neurotransmitter, γ-aminobutyric acid (GABA), although their precise mode of action is unknown. They are known to modulate the release of neurotransmitters including substance P and may exert antitussive effects through attenuation of post-synaptic excitability [9]. In a double-blind, placebo-controlled trial involving patients with chronic cough, gabapentin was associated with a greater improvement in cough-specific quality of life and a greater reduction in cough severity relative to baseline than was placebo [10]. However, the benefit of gabapentin was no longer present at 4 weeks after cessation of the treatment. Vertigan et al. [11] conducted a randomised, double-blinded, placebo-controlled trial comparing the effects on chronic cough of pregabalin with speech therapy versus speech therapy and a placebo. Eighteen patients completed speech therapy and pregabalin, whereas 17 had speech therapy and a placebo. Both arms had improved cough-related quality of life, cough severity and frequency at the completion of the 14 weeks of treatment. However, clinical experience suggests that the response is highly variable, and or many patients, the adverse effects, including sedation and

dizziness or unsteadiness, may outweigh any benefits. Thus, gabapentin and the related anticonvulsant pregabalin require individualised dose adjustments to establish a balance between adverse effects and efficacy. Although no serious complications are reported, adverse effects are common, necessitating appropriate counselling when initiating treatment.

13.2.3 Amitriptyline

Amitriptyline is used for the treatment of depression and lower doses are also prescribed for the treatment of chronic neuropathic pain. This drug is an inhibitor of serotonin re-uptake but may also have effects on the muscarinic, adrenergic and histaminergic systems [12]. A randomised controlled trial by Jeyakumar et al. [13] looked at the effect of amitriptyline compared to opioids. Most of the patients (15, 87%) who received amitriptyline reported ≥50% reduction in their cough, compared to only one of 13 patients in the opioid group. Amitriptyline was also associated with improved cough-related quality of life [13]. However, in another study conducted over a longer duration (2 months), the efficacy of amitriptyline in patients with chronic cough was short-lived, and the majority of subjects discontinued treatment [14].

13.2.4 Tachykinin Receptor Antagonists

The tachykinins, substance P, neurokinin A and neurokinin B are released both from the peripheral endings of afferent nerves (predominately C-fibres) and from central neural structures. The tachykinin receptor, neurokinin 1 (NK1) receptor has gained attention as a target for chronic cough treatment. The NK1R antagonist, Aprepitant, has been shown to reduce cough in patients with lung cancer [15]. A pilot study of Serlopitant, a centrally acting NK1R antagonist, resulted in significant improvements in objective cough frequency and sustained reductions in daytime cough frequency [16]. Currently, Serlopitant and Orvepitant, another NK1 receptor antagonist, are undergoing further clinical evaluation.

13.3 Treatments with a Peripheral Site of Action

Sensory nerves of the airways express a variety of receptors/channels that when activated trigger cough. Therefore, it seems logical that these receptors/channels may represent therapeutic targets for cough.

13.3.1 Transient Receptor Potential (TRP) Channel Inhibitors

Ion channels present on respiratory vagal afferent nerve termini can be activated by a wide variety of stimuli to elicit cough and other reflexes. The main family of ion channels implicated in the initiation of sensory reflexes are the transient receptor

potential (TRP) channels, and of particular interest in relation to cough are members of the Vanilloid (TRPV1, TRPV4), Anykrin (TRPA1) and Melastatin (TRPM8) families [17]. Capsaicin, the active ingredient of chilli pepper, binds TRPV1 receptors causing pain, burning sensation, cough and urge-to-cough, and is one of the most potent tussigenic agents used in inhalation cough challenges [18]. TRPV1 is expressed by vagal afferent C and Aδ-nociceptive fibres innervating the airways [18] and TRPV1 receptor expression is increased in airway nerves of chronic cough patients [19]. However, despite efficacy being predicted in preclinical guinea pig and human in vitro vagal models [17], a potent TRPV1 receptor antagonist failed to significantly alter cough frequency or urge-to-cough in patients with refractory chronic cough in a recent clinical trial [20]. Thus, it is unlikely that TRPV1 will be an effective therapeutic target for chronic cough. TRPA1 receptors are also present on vagal sensory afferents and bind a wide range of irritants (but not capsaicin) present in tussigenic environmental pollutants, such as cigarette smoke, as well as functioning as cold thermosensors [21]. However, despite the preclinical promise of TRPA1 receptors as effective antitussive targets [21], a TRPA1 antagonist did not show significant antitussive effects in humans [22]. TRPM8 is activated by cooling compounds such as menthol and eucalyptol. Although thought to play a role in cough induced by the inhalation of cold air, the TRPM8 agonist menthol also has protective and soothing effects and is a component of many over-the-counter cough remedies [23]. The evidence for an antitussive role of TRPM8 is inconclusive and modulation of TRPM8 remains to be investigated as a potential target for chronic cough.

13.3.2 Purinergic Receptor Antagonists

Purinergic receptors include subtypes of P2X ion channel receptors which are activated by ATP and have received considerable attention recently as potential targets for the treatment of pain and cough. P2X3 receptors are relatively specific for adenosine triphosphate (ATP), release of which is triggered by tissue inflammation and present in increased concentrations in the airways of chronic smokers and in chronic obstructive pulmonary disease [24], after allergen challenge in asthmatics [25], and in fibrotic interstitial lung disease [26]. In animal model of pain, P2X3 receptors expressed on airway sensory afferent nerves may play a role in central sensitisation to pain including inflammatory hyperalgesia and mechanical allodynia [27]. However, ATP administered to the bronchial tree does not cause a dramatic left-shift in cough reflex sensitivity [28]. Thus, the P2X3 receptor may merely be a link in the chain of cough hypersensitivity rather than the primary mediator [29].

Gefapixant (MK-7264) is a P2X3 antagonist and has been evaluated in patients with refractory chronic cough at doses ranging from 7.5 to 600 mg twice daily. A proof-of-concept study demonstrated efficacy at the high dose of 600 mg bid [30] and subsequent dose-ranging placebo-controlled studies demonstrated efficacy in doses from 15 to 50 mg bid with no apparent efficacy advantage with doses above 50 mg bid [31–33]. Although Gefapixant has generally not been associated with

serious adverse events, dysgeusia, a taste disorder in which a foul, salty, rancid, or metallic taste persists in the mouth, is most commonly reported; of note, the number of patients who reported dysgeusia increased as the dose increased. Although some patients were unable to tolerate the dysgeusia, in the real world, patients could mitigate this adverse effect by changing their dose. Previous preclinical research has identified P2X receptors, particularly P2X2/3 receptors, as playing an important role in the transmission of taste signals [34]. Studies of purinergic P2X2/3 double-genetic knockout mice have demonstrated a loss of taste-evoked activity [35]. Previous studies with Gefapixant suggest a mechanistic role in taste disturbance from P2X3 antagonism based on dose-related taste disturbance [31–33]. Effects on cough reduction were observed in lower doses where taste disturbances were more limited or minimal; Phase 3 studies are ongoing and will provide further evidence of whether positive improvements in the treatment of refractory chronic cough can be achieved with acceptable safety and tolerability. Recently, the effect of Gefapixant on cough reflex sensitivity to evoked tussive challenges (ATP, citric acid, capsaicin and distilled water) was investigated in a small group of patients with chronic cough [36]. The authors found that Gefapixant 100 mg increased cough challenge threshold (either C2 or C5) for ATP and distilled water whereas the drug had no effect on cough thresholds to capsaicin and citric acid. Of note, responses for all challenges in healthy subjects mimicked responses of chronic coughers, but to a lesser degree. Additionally, Gefapixant improved cough severity and frequency among chronic cough subjects [36]. The finding that Gefapixant led to increases in concentrations needed to induce multiple coughs upon ATP exposure is consistent with peripheral target engagement of the ATP-activated P2X3 receptors in the pathophysiology of chronic cough [37]. It suggests that release of ATP by airway cells may directly stimulate afferent nerves causing coughing. However, the rapid metabolism of ATP would imply continuous release of ATP to stimulate P2X3, a receptor with a purportedly rapid desensitisation [38].

The novel, selective P2X3 antagonist DT-0111 has shown to inhibit markedly the activation by ATP of nodose pulmonary vagal afferents in vitro, and, given as an aerosol, to inhibit aerosolised ATP-induced bronchoconstriction and cough in vivo [39]. Large-scale, placebo-controlled trials are needed in humans to evaluate the efficacy and safety of DT-0111 for the control of cough in patients with refractory or unexplained chronic cough.

13.4 Conclusions

Chronic cough is an extremely common clinical problem that can exist in isolation or as the dominant symptom for patients across a wide range of common chronic respiratory conditions. Chronic refractory or unexplained (“idiopathic”) cough is very difficult to treat, as effective antitussive agents are currently limited. Recognising the similarities between chronic cough and chronic pain has led to trials of neuromodulators such as gabapentin and pregabalin that have demonstrated an antitussive effect. There have been important developments in the mechanistic

understanding of cough and elucidating the associated neurobiology, and with this have come a number of promising therapeutic targets. Some of these are at advanced stages of clinical development with drugs targeting the P2X3 receptor most promising. However, many challenges remain and partnerships are required, bringing clinicians and patients, scientists and industry together with government agencies to overcome these. This approach is likely to speed up drug discovery with the ultimate aim of providing better treatments for cough patients.

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