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Pharmacological modulation of cough reflex

GABRIELA NOSALOVA, JURAJ MOKRY, SONA FRANOVA

Abstract

The cough reflex is an attack of powerful expiratory efforts produced by active contractions of the expiratory muscles, preceded by deep inspirations.

Cough is a normal physiological defensive reflex responsible for keeping the airways free of obstruction and harmful substances. However, cough is also the most frequent symptom of acute respiratory system diseases and is the most common reason why sick patients visit physicians. The largest diagnostic group associated with chronic cough is asthma or asthma-like syndromes and chronic obstructive pulmonary disease. Furthermore, gastroesophageal reflux, rhinitis/postnasal drip syndrome and unpleasant side effects accompanying the therapy with angiotensin-converting enzyme inhibitors (ACEI) represent other causes of chronic cough. The cough reflex may be elicited by the activation of receptors of non-myelinated nociceptive A δ -fibers and C-fibers and receptors of myelinated A δ -fibers distributed throughout the respiratory tract. In recent times as proper cough receptors are thought to be rapidly adapting receptors (RARs) of myelinated fibers, C-fibers and transient receptor potential vanilloid 1 (TRPV1) localize on the non-myelinated fibers.

As the pathological cough (especially its chronic form) has significant impact on patient's quality of life, observed either in physical activity or psychosocial domain, various treatment attitudes are used for different forms of cough (acute, subacute, chronic, productive, nonproductive, psychogenic, asthma-associated, or painful).

Interest of research in this field is accompanied with the fact, that many antitussive drugs (mainly from the opioid group), which have been the antitussives of choice for decades, are limited by their unpleasant and very often adverse reactions.

In this chapter the authors divided the drugs used in the pharmacological treatment of cough into several groups. These include the drugs acting at the level of receptors, the drugs affecting the propagation of cough impulses in afferent nerves, the drugs modulating the central coordination of cough reflex, the drugs acting at the level of efferent nerves, and the drugs affecting the effectors. Efficacy of many antitussive agents is connected with their influence on more than one level of cough reflex.

Another group used in the therapy of cough are mucoactive substances that change the dry, irritant and nonproductive cough into the so-called productive cough with nonirritating expectoration. The last-mentioned group in this chapter is demulcerative and hydrating drugs, which can create a defense layer protecting the mucous membranes from other irritant stimuli.

Keywords: *cough reflex, antitussive drugs, mucoactive substances, demulcerative drugs*

Abbreviations: ACE, angiotensin-converting enzyme; ACEI, angiotensin-converting enzyme inhibitors; GABA, gammaaminobutyric acid; LPh, laryngopharyngeal area; MAOI, monoaminoxidase inhibitors;

NEP, neutral endopeptidase; NKA, neurokinine A; NKB, neurokinine B; NMDA, N-methyl-D-aspartate; OTC, over-the-counter; RARs, rapidly adapting receptors; REM, rapid eye movement; SP, substance P; TB, tracheobronchial area; TRPV1, transient receptor potential vanilloid 1.

I. Introduction

Exchange of gases while breathing forms the major role of the lungs. As the inspired air is markedly polluted, the airways are fit for numerous defense mechanisms. The defense of the respiratory system against inhaled particles and gases involves the integration of many complex physiological, biochemical and immunological processes that interact directly with the properties of inhaled materials (Korpas and Tomori, 1979). The various defense mechanisms are integrated to provide local degradation and detoxication, as well as mechanical elimination of both exogenous substances and products of pathological processes from the airways. The most important defensive reflex of the airways is cough, which, together with the mucociliary transport system, forms the main mechanism for cleaning of the respiratory tract (Korpas and Noslova, 1991; Chung and Chang, 2002; Belvisi and Geppetti, 2004).

II. Definition of cough

Korpas and Tomori (1979) characterized the cough reactions as an attack of powerful expiratory efforts produced by active contractions of the expiratory muscles, preceded by deep inspirations. The violent expiration, which provides the high flow, helps to shear away mucus and remove foreign particles from the larynx, trachea and large bronchi.

Cough appears when the membrane lining of the respiratory tract produces excessive mucus or phlegm. These secretions help to protect airways from infections and irritants. Coughing prevents the breathing passages from closing and also prevents infected mucus from falling into lungs and bronchial tubes, which could be very dangerous. In the absence of abnormal sputum production there is likely to be another reason for cough. The probable explanation could be an increased sensitivity of the cough reflex, which leads to an abnormal response to “naturally” inhaled stimuli (Fuller and Jackson, 1990; Reynolds et al., 2004).

III. Epidemiological data

Cough is one of the most frequent symptoms of respiratory system diseases and is the most common reason why sick patients visit physicians in the United States (Bolser, 1996; Ziment and O’Connell, 2002). Cough prevalence in populations depends on smoking prevalence and on the level of air pollution. Statistical data are in the range of 5–40% (Fuller and Jackson, 1990; Irwin and Madison, 2002; Wright et al., 2004). Cough is a common complaint of patients presenting to primary care physicians. Most patients with acute cough have self-limited illnesses like common cold and influenza. Gwaltney (1997) showed that the viral infections represent the most frequent causes of self-limited cough. These viruses include rhinovirus,

coronavirus, parainfluenza virus, respiratory syncytial virus, adenovirus and influenza virus. These viruses can cause a spectrum of diseases including common cold, acute infections bronchitis, bronchiolitis and bacterial pneumonia. According to Gwaltney (1997) the highest incidence of cough occurred in patients with influenza (reaching 70% on day 3 of the illness) and rhinovirus colds (approximately 35% over the 7-day period of illness). Antitussive drugs such as codeine and dextromethorphan are among the most commonly used prescription and over-the-counter (OTC) drugs in the world (Choudry and Fuller, 1992). The widespread use of antitussive medications for the treatment of cough associated with upper respiratory tract infection generates many millions of dollars for the pharmaceutical industry (Eccles, 1996). In the UK, the cough/cold market accounted for £350 million, whereas in the USA, well over \$2 billion was spent on OTC medicines (Morice, 2001). These facts demonstrate the vast socio-economic consequences of acute cough.

Chronic cough is one of the most common symptoms presenting to respiratory physicians and affects 10–38% of patients (Hsu et al., 1994). The largest diagnostic group is asthma or asthma-like syndromes. A second large group connected with cough is gastroesophageal reflux (Plutinsky et al., 1998). Rhinitis/postnasal drip syndrome represents another cause of chronic cough. Predominantly this kind of cough seems to occur (3–40%) accompanied by unpleasant side effects due to therapy using ACE inhibitors (Kubota et al., 1996).

IV. Physiology of cough reflex

Cough reflex may be elicited by the activation of non-myelinated C-fibers and myelinated A δ -fibers distributed throughout the respiratory tract (Fox, 1996a,b; Reynolds et al., 2004). These nerve endings have strictly vagal origin. They are located underneath the airways epithelium and demonstrate high sensitivity to inhaled irritants. Coughing is a reflex activity initiated by stimulation of sensory nerves in the lining of the respiratory passages, the tubes we use to breathe. Coughing can be induced from the larynx and tracheobronchial tree, but not directly from structures above or below these sites (Widdicombe, 1998). In a healthy man, cough is present only when, for example, an insufficiency of mucociliar apparatus and alveolar macrophages prevents them from fulfilling their cleaning role in airways. An example of such a situation could be when solid or liquid food particles accidentally get into the airways, or through inhalation of irritant gases (Widdicombe, 1995).

Knowledge of structures participating in the genesis of this defense mechanism is potentially important for antitussive therapy, because the mechanism of both peripherally and centrally acting antitussive drugs may depend on the identity of the afferent pathways involved.

V. Larynx and pharynx – laryngopharyngeal cough

The larynx, being the sentinel of the lungs, possesses abundant sensory innervations, which can produce violent coughing after their activation. Afferent activity may be elicited from the larynx by mechanical and chemical irritants. Most of the sensory

traffic from the larynx is conveyed in the superior laryngeal nerves (Fuller and Jackson, 1990; Sant'Ambrogio and Sant'Ambrogio, 1996). Three types of receptors – pressure, drive and cold – take part in a clear respiratory modulation. Pressure receptors respond to changes in trans-laryngeal pressure, drive receptors are stimulated by passive or active motion of the larynx and cold/flow receptors respond to a decrease in laryngeal temperature. Although respiratory-modulated receptors play an important role in the function of the upper airways, they are not generally viewed as a primary factor in the elicitation of cough reflex. There are two types of receptors localized in laryngeal mucus, both of which are connected with the cough reflex. These are:

Rapidly adapting receptors (RARs) or irritant receptors. The cough reflex is probably caused by the stimulation of the irregular firing irritant receptors. They are usually silent in quiet breathing and activated only by mechanical and chemical irritant stimuli (e.g. cigarette smoke, distilled water, CO₂, etc.), the prompt blocking effect of topical anesthetics are thought to have a superficial location (Widdicombe et al., 1988). Laryngeal irritant receptors are stimulated by halothane (which inhibits those receptors in tracheobronchial tree) and by water solutions lacking chloride anions (Anderson et al., 1990; Sant'Ambrogio, 1996), but not by hyposmolar solutions in the trachea (Ventresca et al., 1990).

C-fiber receptors. They are sensitive to mechanical stimulation, cooling, chemical stimulation by capsaicin and phenylbiguanide. However, we must respect the existence of considerable differences in species.

The characteristic signs of the laryngopharyngeal cough are active expirations and several fast and powerful inspiratory movements. It differs from tracheobronchial cough in the presence of the inspiratory component, which is in this case as strong as, or even stronger, than the active expiratory component (Figure 1). From the pharmacological frame of reference, this type of cough is more resistant to cough suppressant agents. From our long-standing results we can conclude that the influence of antitussive agents varies very strongly. We found that some of the substances can suppress the cough from the laryngopharyngeal area more potently than the others, which were more effective in tracheobronchial cough suppression (Table 1).

VI. The tracheobronchial tree – tracheobronchial cough

There are three types of sensory nerve endings in the tracheobronchial region of the respiratory tract:

(a) *Rapidly adapting stretch receptors (RARs) or “irritant” receptors.* Regarding the cough reflex this type of receptor seems to play a very important role. RARs respond to mechanical and chemical stimuli (prostaglandin E₂, histamine, cigarette smoke etc.). All of the stimuli that can induce coughing are able to stimulate RARs, although most of them activate bronchial C-fiber receptor, too (Karlsson, 1996; Reynolds et al., 2004). “Irritant” receptors are situated within the mucosal surface of the major airways in high concentrations, especially at bifurcations. These places are responsible for mucus clearing and expelling foreign materials from the airways. Myelinated fibers in the vagal nerves conduct the sensory information. It is interesting that some viral infections can enhance their sensitivity to stimuli, causing the cough (Empey et al., 1976; Chung et al., 2003).

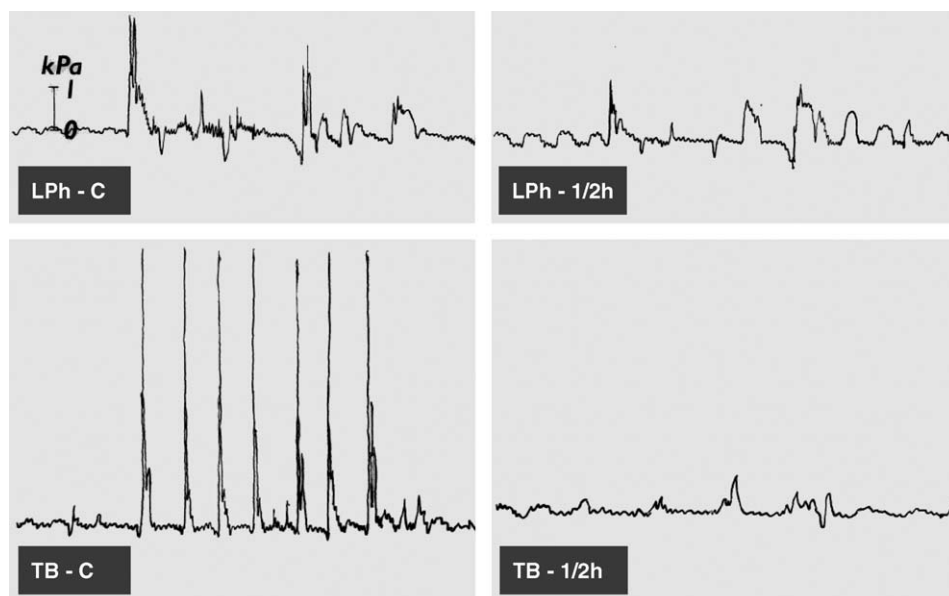


Fig. 1. Cough records from laryngopharyngeal (LPh) and tracheobronchial (TB) areas of the airways before (C, control) and 30 min after (1/2 h) application of codeine in dose of 10 mg/kg i.p.

Table 1

Substances divided according to the area with stronger effect. LPh – laryngopharyngeal, TB – tracheobronchial area of the airways

Higher efficacy in LPh area	Higher efficacy in TB area
Procaine	Tramadol
Azipranon	Tilidin
Glaucine	Pentazocine
Butamirate citrate	Codeine
Dropropizine	L-propoxyphene
Isoprenaline	Dextromethorphan
Guaifenesin	Silomat
Diazepam	Gabalid

(b) *Slowly adapting stretch receptors*. These are located in the membranous posterior wall of conducting airways within the smooth muscle. They are supposed to be important for the act of coughing.

(c) *Tracheobronchial C-fiber receptors*. The stimulation of bronchial C-fiber receptors can cause cough, as well as apnea and bronchoconstriction, presumably in response to different varieties or concentrations of stimulants. All the stimuli used for irritation of C-fiber receptors can also activate RARs. Many cough-inducing chemical stimuli (like bradykinin, sulfur dioxide and capsaicin) may act directly on the RARs, but in addition they can activate C-fiber receptors, which release

tachykinins. These will in turn act on postcapillary venules, causing plasma extravasations and stimulation of adjacent RARs. The increase in interstitial liquid volume might also affect the structure of epithelium and stimulate the branches of RARs there (Widdicombe, 1995). In recent times TRPV1 receptors have been identified on A δ nociceptive fibers, which under normal physiological conditions do not synthesize neuropeptides, but can be activated by capsaicin. Reynolds et al. (2004) suggested that C-fibers do not incite cough per se but might be involved in the sensitization of the cough reflex.

(d) *Pulmonary C-fiber receptors.* Raj et al. (1995) showed that pulmonary C-fiber receptors cause cough in unanesthetized humans. However, further experiments are needed for wider acceptance of this fact.

VII. Central nervous mechanisms in cough

There is clear evidence that airway sensory afferents, irrespective of whether they are myelinated or non-myelinated, terminate within the brainstem, in the nucleus tractus solitarius (Jordan, 1996, 1997; Takahama, 2003). Vagal afferents have been shown to contain mediators such as glutamate and 5-hydroxytryptamine. It is also a well-known fact that NMDA receptors, opiate receptors and 5-HT receptors are able to modulate transmission through the nucleus tractus solitarius. This region is anatomically adjacent to the area postrema, where the blood–brain barrier is weak or absent, so antitussive drugs given peripherally could be acting at the central site, on the sensory side of the system. Other areas, such as nucleus ambiguus and dorsal vagal nuclei, also contain these types of receptors and could be considered as additional sites of action. Apart from this, activation of NMDA receptors and both the opioid and serotonergic systems can modify the central respiratory network (Chung et al., 2003). This is also supported by our results with substances known for their ability to influence these receptors (Figure 2; Nosalova, 1998). The antitussive actions of these agents may occur via this respiratory action (Kamei, 1996).







	Codeine	Dextromethorphan	Clobutinol
LPh			
TB			

Fig. 2. Centrally acting antitussive drugs – comparison of antitussive activity. Codeine – opiate receptor antagonist 10 mg/kg i.p., Dextromethorphan – NMDA receptor antagonist 2 mg/kg i.p., Clobutinol 20 mg/kg i.p. LPh – laryngopharyngeal and TB – tracheobronchial area of the airways.

Despite huge endeavors of experimental researchers, all of the neurochemical processes participating in the mechanism of action of antitussive agents are still not known. Hedner et al. (1980) highlight an important role of gammaaminobutyric acid (GABA) in tonic modulation of respiratory activity. As the breathing and cough centers are tightly associated, we decided to verify the ability of gabaergic substances to influence the cough reflex. We obtained original priority results (Nosalova et al., 1986a,b, 1987), which support the statement that gabaergic substances are able to suppress cough (Figure 3) and that gabaergic mechanisms can take part in mechanism of action of other cough-suppressing agents.

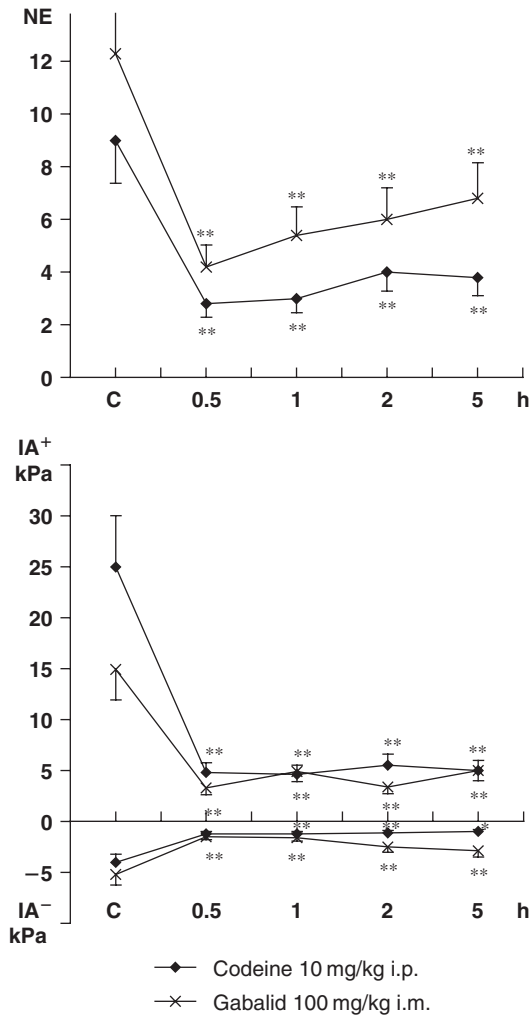


Fig. 3. Antitussive effect of Gabalid (gabaergic receptor agonist) compared to codeine. NE – number of cough efforts after mechanical stimulation of tracheobronchial area of the airways, IA⁺ – intensity of cough attack in expirium, IA⁻ – intensity of cough attack in inspirium, C – control, 0.5, 1, 2, 5 h – time after administration of tested substance.

VIII. Pathophysiology of cough

Cough is considered to be a pathological reflex from the moment it stops fulfilling its cleaning role and starts to burden the patient. Pathological cough (especially its chronic form) has a significant impact on the patient's quality of life, observed either in physical activity or in the psychosocial domain. Coughing patients suffer often from insomnia, exhaustion, nausea and emesis, worsening of performance at work or incontinence. In many of them it can lead to social problems connected to the need for changing or leaving a job or important social activities (Irwin, 2001). In addition to this, the intrathoracic pressure changes during the cough (inspiration -13 kPa and expiration $+30$ kPa) can cause costal fractures, cough syncope, pneumothorax, pneumomediastinum, herniation, etc. Patients with coronary lesions may experience anginal pain. Cough also represents one of the ways for transmission of infections (Korpas and Nosalova, 1991).

The most frequent cause of abnormal cough reaction is the presence of pathological processes in the respiratory system, leading to increased irritability of afferent nerve endings or increased sensitivity to different stimuli (Schuligoi et al. 1998; Shinagawa et al., 2000). These conditions can be found during inflammatory diseases of upper and lower airways of either viral or bacterial origin.

IX. Cough and inflammation

Inflammatory process in the airways increases mucus production, which, owing to impaired mucociliary transportation, could be one of the reasons for mechanical irritation. However, more important is the fact that accumulated phlegm rich in inflammatory cells and mediators functions as a cough-provoking chemical stimulus.

Many inflammatory mediators may modulate cholinergic and sensory nerves in the airways through the activation of receptors on nerve terminals (Barnes, 1992; Reynolds et al., 2004). Sensory nerves in the airways contain several neuropeptides – the tachykinins. The main members of this family are substance P (SP), neurokinin A (NKA) and neurokinin B (NKB), among which substance P is the best known. Stimulation of these nerves causes a constellation of responses known as neurogenic inflammation. Distribution of substance-P-containing nerves is close to that of the RARs mediating cough in the airways (Hay, 2001). The most important enzyme for the breakdown of SP in these nerve fibers has been found (Sekizawa, 1996). Neutral endopeptidase (NEP) is a key enzyme in the degradation of tachykinins in the airways. This enzyme is strongly expressed in epithelial cells (Barnes, 2001). In humans, aerosol of SP did not cause cough at the concentration of up to 10^{-5} M in normal subjects, but they did in patients with upper-respiratory tract infection (Katsumata et al., 1989).

Another factor, the attenuation of the barrier function of the airways epithelium, is involved in the inflammation. This way, the irritants can get to the nerve endings more easily. This process is aggravated by total destruction of epithelial cells, leading to loss of another important role – production of NEP.

During inflammation of the airways, damaged epithelium is not able to form NEP, which may facilitate the penetration of substance P. Fox (1996b) showed, that SP

causes cough by direct stimulation of rapidly adapting pulmonary stretch receptors (RARs). Apart from this, tachykinins and especially SP also showed indirect activity resulting in cough reflex facilitation (Advenier, 1996). SP stimulates mucus secretion from submucosal glands and mediates the increased plasma exudation and the vasodilator response to tachykinins. Tachykinins also enhance cholinergic neuro-transmission by facilitating acetylcholine release at cholinergic nerve terminals and by enhancing ganglion transmission (Watson et al., 1993). A variety of species, including human tachykinins, stimulate C-fiber receptors and rapidly adapting pulmonary stretch receptors and can cause cough (Widdicombe, 1996). Tachykinins may also interact with inflammatory and immune cells.

Besides the mechanism mentioned already, increased sensitivity of the afferent nerve fibers can also cause the genesis of pathological cough. This occurs when in an individual a dry cough is response to such concentrations of tussigen stimuli, which in normal healthy individuals do not provoke cough response. O'Connell (2001) showed that the cough reflex is "upregulated" in persistent dry cough. This upregulation occurs at the level of the afferent cough receptors in the airways. These are the action site of the most important drugs, which lead to downregulation of the abnormally sensitive cough receptors.

Increased as well as decreased reactivity of afferent nerve endings, leading to the so-called ineffective type of cough, is considered to be a pathological state (Laurence et al., 1997; Korpas and Tomori, 1979). The other reasons for this type of cough may be central structures disorders, which take part in cough reflex regulation, or disorder of effectors mechanisms. The consequence of ineffective cough can manifest in development and intensification of pathological processes in the airways (Nishino et al., 1996).

Understanding the mechanisms participating in cough-reflex genesis, (especially the cough with pathological character) enables its appropriate treatment. The cough, fulfilling a physiological role and cleaning the airways of accumulated secretions, phlegm, tissue detritus, dirt and foreign bodies in the airways and the ciliary mechanisms cannot be pharmacologically influenced (Nosalova et al., 1989; Sada, 1997). The best we can do is to help with expectoration (Nosalova et al., 1986a,b, 1998). On the contrary, the pathological type of cough has to be influenced pharmacologically. We can suppress it, hold it at an acceptable level, or modify its effectiveness.

X. Curiosities of cough reflex

The cough reflex with its characteristics is one of the strangest reflexes of all. It is one of the airway-defense reflexes and also can be evoked voluntarily (Lavigne et al., 1991; Lee et al., 2002). Hutching et al. (1993) showed that cough could be not only initiated but also inhibited by conscious control. There is also evidence, that cough can only occur during consciousness and does not occur during REM phase of sleep (Anderson et al., 1996). Cough is the first respiratory response inhibited by general anesthesia without any prior slowing down of respiratory rate.

From the clinical aspect it is particularly important that cough is present as a symptom by most respiratory system diseases (Nosal and Banovcin, 2001; Chung

et al., 2003). Cough is often registered as the only symptom of respiratory diseases (Koh et al., 1999).

The particularity of cough reflex is determined also by the fact that if it is disproportionately intensive or persisting, it changes to a pathological reflex and starts to burden the patient. It disturbs daily activities like sleep, food intake, normal breathing and circulation and disables the individual in society by noise or by incontinence. This leads to a significant worsening of the quality of the patient's life. Cough can induce complications, that will jeopardize human life. Therefore, this pathological kind of cough has to be suppressed or held at an acceptable level (Korpas and Nosalova, 1991; Nosalova, 1998; Nosalova et al., 2004).

Another particularity of cough reflex could be its adverse action on normal physiology. The increased activity of muscles involved in breathing leads to increase in intake of oxygen. When oxygen supply is impaired owing to principal respiratory system disease, the tissues are lacking it.

Cough is a reflex that may be initiated voluntarily without any input from afferent vagal fibers. Conversely, cough induced by incoming vagal impulses may be voluntarily suppressed (O'Connell, 2001).

XI. Cough forms

Depending on the cause and duration, cough can be divided into three categories: acute cough, lasting less than three weeks; subacute cough, lasting three to eight weeks; and chronic cough, lasting more than eight weeks. Since all types of cough are acute at the outset, it is the duration of the cough at the time of presentation that determines the spectrum of likely causes. Depending on the phlegm (mucus) production, the cough can be called as dry or wet (productive) (Parvez et al., 1996). Painful cough, the name for the pain-eliciting cough, sometimes accompanied by symptoms of various pathological processes in the respiratory tract such as bronchial asthma, chronic bronchitis, bronchogenic carcinoma, gastroesophageal reflux, etc. It could possibly have a psychogenic basis (Lavigne et al., 1991). Cough can occur as an adverse effect of drug treatments, e.g. after the administration of ACEI (Franova and Nosalova, 1998; Gajdos and Huttova, 2002).

XI.A. Acute cough

Acute cough is mostly mild and lasts for a very short time (up to 21 days). It occurs during acute diseases of respiratory tract caused especially by viral infections, common cold, acute bacterial sinusitis, exacerbations of chronic obstructive pulmonary disease, allergic rhinitis, rhinitis due to environmental irritants and pertussis. In the initial phase it is non-productive (dry), but it can later change into a productive one. Its duration is usually several days and it weakens gradually. This kind of cough often does not need to be modulated therapeutically, as the drugs have no impact on disease outcome (Irwin et al., 1993; Chung et al., 2003). The drugs are recommended if the cough attacks are too frequent and so significant that they extensively lessen the patient's comfort, or if the cough is persistent and painful. In these situations, drugs that suppress and lower the irritation of inflamed mucous membranes are used

facilitating daily comfort and tranquil sleep (Braga and Allegra, 1989; Kurz, 1989; Korpas and Nosalova, 1991; Parvez et al., 1996).

Korppi et al. (1991) recommended that the use of antitussives in children should be restricted to such situations where their efficacy has been proven, i.e. in the treatment of chronic non-productive cough.

For treatment of this form of cough we recommend a combination of older-generation H₁ antihistamines and nasal decongestants. For patients who cannot take and tolerate this combination it is possible to use intranasal ipratropium bromide (0.06% spray). The newer generation of antihistamines is ineffective for treatment of cough caused by common cold. These agents are effective when cough is a symptom during histamine-mediated conditions such as allergic rhinitis. In this case we can also use nasal cromolyn and corticosteroids. Irwin and Madison (2000) recommend the usage of antibiotic therapy for patients with exacerbations of chronic obstructive pulmonary disease (if acute cough is accompanied by worsening shortness of breath, wheezing, or both), acute bacterial sinusitis, pneumonia and *Bordetella pertussis* infection. We deem it very important to say that antibiotic treatment should not be determined generally, such as for 3 weeks, but should be individualized. The duration of the treatment depends on symptoms, remission and normalization of patient's health constitution (well-being).

XI.B. Subacute cough

If the cough lasts for 3–8 weeks, it is considered to be the subacute form of cough. The treatment of this kind of cough is based on the elimination of the cough-provoking cause. Practically, it does not differ from the treatment of chronic form of cough. For elimination of subacute form of cough we use older-generation antihistamines combined with nasal decongestants, ipratropium bromide, bronchodilators from the group of β -agonists, corticosteroids, antitussives and the target antibiotic treatment, if necessary.

XI.C. Chronic cough

Chronic cough is defined as a cough that lasts for more than three weeks (Irwin et al., 1990; Cap, 1999). Many physicians accept a longer limit: such as six to eight weeks. As for diagnosis, this form of cough signals the possibility of serious disease, such as chronic bronchitis, bronchial tumor, lung abscess, blood stasis in small circulation, etc. According to Philp (1997), more than 90% of cases of chronic cough are a result of five common causes: smoking, postnasal drip, asthma, gastroesophageal reflux and chronic bronchitis. We prefer specific therapy in the treatment of chronic cough (Table 2). The success of the specific therapy depends on the correct diagnosis of the cause of the cough mechanisms, that arouse it (Korpas and Nosalova, 1991; Bolser, 1996; Nosalova, 1998; Nosalova, 2001).

Symptomatic treatment of chronic cough (also called nonspecific therapy) is indicated only in cases where the cough does not fulfill its role and the complications could represent real or possible danger for the patient (Korpas and Nosalova, 1991; Irwin et al., 1998). We prefer the drugs from the group of non-narcotic antitussives with peripheral site of action (Table 3). In our conditions these drugs showed lower

Table 2
Management of chronic cough

Cause	Therapy	Remark
Cigarette smoking	Cessation of smoking	Leads to a dramatic decrease in cough within 1 month
Occupational exposure (e.g. dust, fumes, other irritants)	Reduction of exposure	Wearing a face mask, improving air circulation, a change of job may be necessary
Postnasal-drip syndromes Nonallergic rhinitis	Combination of older-generation of antihistamines and decongestants	Newer generation of histamine antagonists are inferior in treating cough but avoid sedation
	Ipratropium (0.06%) nasal spray for 3 weeks	Mainly for patients who cannot take the older-generation of antihistamines
	Nasal steroids	Nasal steroids should be added, if cough is not controlled by antihistamine-decongestant medication or persist 1–2 weeks
	Vasoconstrictor e.g., oxymetazone	Vasoconstrictor should not be used for more than 5 days
Chronic bacterial sinusitis	Antibiotics Older-generation antihistamine-decongestant combination	If sinus infection is suspected, appropriate antibiotics may also be ordered. The selection and duration of the antibiotic treatment is individual.
Allergic rhinitis	Avoidance of offending allergens, Newer-generation antihistamines	
Hypersensitivity that follows an upper respiratory infection (as in the so-called cough variant asthma)	Antihistamines, inhaled steroids – if unresponsive to treatment with an antihistamine, dextromethorphan or codeine	Present only on a chronic, usually non-productive cough, a positive result on metacholine challenge, physical examination out of periods with acute symptoms is essentially normal
Chronic bronchitis	Discontinuation of smoking Avoidance of environmental irritants and toxins	In this case we prefer ipratropium in the therapy of cough, because it decreases mucus production, dilates the bronchi and is more effective in the therapy of cough than beta-agonists

Table 2 (continued)

Cause	Therapy	Remark
	Preventive health measures (e.g. immunizations with pneumococcal vaccine, annual influenza vaccinations)	
	Treatment of community-acquired respiratory infections	
	Optimal bronchodilatory therapy,	
	Postural drainage and hydration,	
	Correction of malnutrition,	
	Oral steroid therapy, if it is necessary	
Asthma bronchiale	Inhaled ipratropium Avoidance of allergens, Prophylactic inhalation: Cromolyn, Beta-agonist and/or Steroid inhalers, or Oral corticosteroids, if required	Typical syndromes: —dyspnea —coughing —wheezing Some times it is necessary to have long-term maintenance therapy with anti-inflammatory drugs.
Drugs induction: -Angiotensin-converting enzyme inhibitors (ACEI)	-Withdrawal of drug, -Sulindac, -Indometacin, -Calcium channel blockers (e.g. nifedipine, diltiazem), -Alternative class of drugs,	Cough occurs in 5–20% of patients treated with ACEI,
Beta blockers	-Withdrawal of drug, -Substitute a drug from a different class	Beta-blockers can cause increased airway resistance resulting from unopposed parasympathetic activity
Gastroesophageal reflux (GERD)	High doses of proton-pump inhibitors, e.g. omeprazole -Anticholinergic drugs -Calcium channel blockers -Theophylline -Other muscle relaxants -Protective agent, e.g. sucralfate -Prokinetic agent, e.g. metoclopramide or cisapride before meals and at bedtime	Omeprazole, in a dose of 80 mg per day As is necessary As is necessary As is necessary As is necessary Sucralfate may be helpful in a dose of 1 g taken one hour before meals Metoclopramide or cisapride may be added before meals and at bedtime, necessary to avoid eating or drinking for 2 h before sleeping

Table 3
Classification of peripherally acting antitussive drugs

Peripherally acting antitussives	
Butamirate citrate	Intussin Sinecod Tussin
Butamirate citrate + guaifenesin	Stoptussin
Dropropizine	Ditustat
Pentoxyverine	Sedotussin
Prenoxdiazine ^a	Libexin

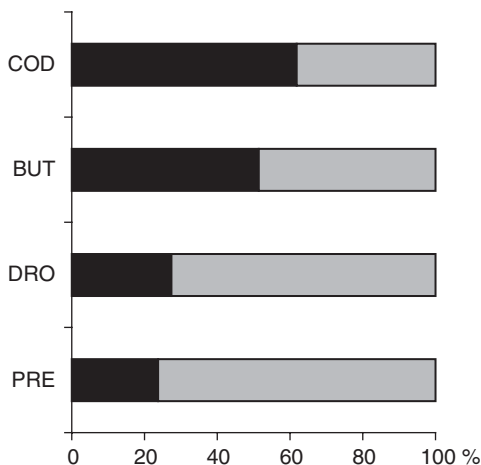


Fig. 4. Antitussive activity of peripherally acting antitussive agents compared to codeine. COD – codeine 10 mg/kg i.p., BUT – butamirate citrate 5 mg/kg i.p., DRO – dropropizine 100 mg/kg i.p., PRE – prenoxidiazine 30 mg/kg i.p.

antitussive activity than the so-called codeine-type agents (Figure 4), but their administration was not associated with unwanted effects. From the centrally acting drugs we prefer agents from the group of synthetic morphine derivatives, or clobutinol (Table 4, groups B and C).

XI.D. Nonproductive cough

Dry, irritant, nonproductive cough significantly burdens the afflicted patient. The cough usually repeats, as rapid air expulsion irritates tracheal as well as tracheo-bronchial mucous membranes. In this situation the cough must be suppressed by antitussives. Codeine showed especially high efficacy (Figure 5). Adding of expectorants is also very useful. They diminish the cough by increasing the fluid content in the respiratory tract and hence calm the mucous membranes of the airway, helping the patient to breathe (Korpaš and Nosalova, 1991).

Table 4
Classification of centrally acting antitussive drugs

Centrally acting antitussives		
A. Opium derivatives and alkaloids	Codeine	Codein
	Combined preparations	Ipecarin
		Benadryl with codein
		Benadryl N with codein
		Codipront
		Kodynal
	Etylmorphine	Diolan
	Pholcodine	Neocodin
		Evaphol
		Galenphol
	Pholcomed	
B. Synthetic morphine derivatives	Dextromethorphan	Cosylan
		Pertussin robittussin
		Rhinotussal
C. Other substances	Clobutinol	Silomat

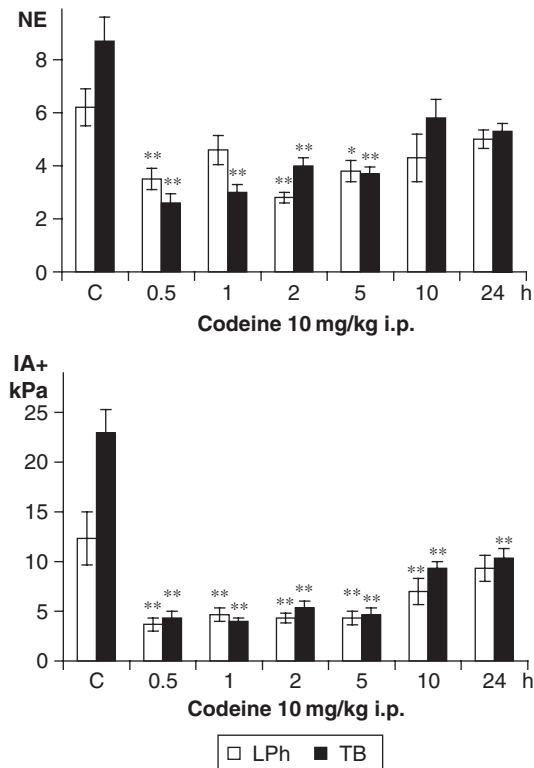


Fig. 5. Effect of codeine in suppression of mechanically induced cough. NE – number of cough efforts, IA⁺ – intensity of cough attack in expirium, LPh – laryngopharyngeal and TB – tracheobronchial area of the airways, C – control, 0.5, 1, 2, 5, 10, 24 h – time after administration of codeine in dose of 10 mg/kg i.p.

XI.E. Psychogenic cough

Nonproductive, irritating cough characterizes psychogenic cough. Its incidence is very often in young people during pubescence, often after an underlying disease subsides. It can occur without any clear cause (Hutching et al., 1993). This form of cough does not respond to antitussive or other therapy and is typically not present during eating or talking. If the patient feels that he is being observed, the cough accentuates. Agents from the group of anxiolytics such as guaifenesin (Guajacuran, Figure 6), or combinations of anxiolytics, with antitussives like guaifenesin + butamirate citrate in Stop-tussin are used in the treatment of psychogenic cough (Nosalova et al., 1986a; Korpas and Nosalova, 1991; Parvez et al., 1996). We found very strong cough-suppressive effect in benzodiazepine and phenothiazine derivatives (Figure 6). These agents could also be used in the treatment of cough induced by psychogenic factors. In addition, antitussive action could be beneficially used for its tranquilizing effect. At the same time we have to be very careful while administering these drugs in patients who need to enforce expectoration. Special attention must be granted to diazepam ordination in pediatric practice, because in acute respiratory diseases associated with fever it very often used to be a part of polyvalent therapy. Its application could lead to suppression of breathing, consecutive phlegm stasis and global worsening of health of the patient. Psychotherapy, is very useful too. But the essential condition is to take the patient away from the surroundings in which he coughs.

XI.F. Cough in asthma bronchiale

Bronchial asthma is very often characterized by the only one symptom – irritant, nonproductive cough, which very often precedes the classical symptoms picture of asthma. In these cases the use of drugs from the group of beta₂-sympathomimetics or corticosteroids (Bush, 2002; Nosal, 2003) that also suppress the cough in allergic patient with bronchial hyperresponsiveness is recommended (Barnes, 1996; Hupka et al., 1996). Beta₂ sympathomimetics, similar to other bronchodilators (Zibolen et al., 1999), can reduce bronchial hyperresponsiveness, stimulate mucociliary clearance and increase water and ion flow into bronchial lumen. This leads to enforcing of

%	NE		IA ⁺		IA ⁻	
	LPh	TB	LPh	TB	LPh	TB
GUI	51,8	31,8	58,7	47,5	43,5	47,2
DIA	33,4	26,9	38,6	45,4	38,3	11,3
CHL	29,0	39,5	52,1	55,8	44,3	46,5

Fig. 6. Antitussive effects of guaifenesin 100 mg/kg i.p. (GUI), diazepam 0.3 mg/kg i.p. (DIA), and chlorpromazine 5 mg/kg i.p. (CHL) estimated by mechanically induced cough in conscious cats (% of decrease). NE – number of cough efforts, IA⁺ – intensity of cough attack in expirium, IA⁻ – intensity of cough attack in inspirium, LPh – laryngopharyngeal and TB – tracheobronchial area of the airways.

expectoration of viscous secretions. Many authors advise a combination therapy of beta₂-sympatomimetics with dextromethorphan in the cough therapy of asthmatics.

XI.G. Productive cough

Productive cough must not be completely suppressed when the retention of secretions could occur, leading to a worsening of the global health constitution of the patient or to the development of pneumonia or atelectasis (Braga et al., 1989; Fox, 1996b; Parvez et al., 1996). In some cases, productive cough can be hyperactive and often repeating. It burdens the patient and disturbs the sleep. The reduction of cough frequency and intensity by expectorants or antitussive–expectorant agents, respectively, is indicated in this situation (butamirate citrate – Sinecod, guaifenesin + butamirate citrate – Stoptussin, ephedrine – Solutan, Ipecarin, etc.). Mucoactive agents are also very useful (bromhexine – Bromhexin, Bisolvon, ambroxol – Mucosolvan, carbocysteine – Mucopront, etc.), as they reduce the phlegm viscosity (Table 5). Furthermore, it is advisable to add agents from the group of secretomotorics to the therapy, which act by inducing of more effective phlegm expulsion from lower parts of the respiratory tract (Braga et al., 1989; Korpas and Nosalova, 1991; Rubin, 2003). Also many plant extracts and derivatives exert their antitussive effect by expectorant and mucolytic activity (see next chapter – Franova et al.: Phytotherapy of the cough).

XI.H. Painful cough

There are certain kinds of cough owing to which the patients feel pain in the throat or in the chest, especially behind the sternum. Painful cough is observed in pleuritis and lung cancer (Homsí et al., 2001). Out of our results (Figure 7) arises the unambiguous fact that in these patients, the group of antitussives with analgesic activity (Nosalova et al., 1985), represents the best therapy for suppression of cough. Alternatively, analgesics with a cough-suppressive effect (tilidine chloride – Valoron, tramadol – Tramal, pentazocine chloride – Fortral, and butorphanol – Beforal) may be used. As in these diseases analgesic agents are often prescribed for pain relief, they can simultaneously and adequately suppress cough as well as pain (Strapková et al., 1987, 1988).

XII. Choice of drugs

The drugs that selectively inhibit or lessen cough reflex are called antitussive agents. The moderation of cough is a result of the reduction of number or frequency of cough efforts, a decrease in their intensity, or both (Empey, 1996). Pharmacologically, it is very important to know that cough as a reflex can be modulated by agents acting at various levels of the reflex arc: at the level of receptors, afferent nerves, cough center, efferent nerves and effectors, as well as by alteration of bronchial secretion (Reynolds et al., 2004). Some agents are able to influence more levels, with predominance in one of them.

XII.A. Drugs acting at the level of receptors

According to the thinking nowadays, cough reflex is triggered by the irritation of nerve endings that are present under the airway mucous membrane. They are called rapidly adapting irritant receptors and mediate the cough reflex after mechanical stimulation. In smaller bronchi there is another group of epithelial receptors with medially rapid adaptive ability. These receptors mediate the cough evoked by chemical stimuli (Widdicombe, 1995).

The anatomical localization of cough receptors in the airways enables the use of local anesthetics (Nosálova and Strapková, 1989; Reynolds et al., 2004), which could

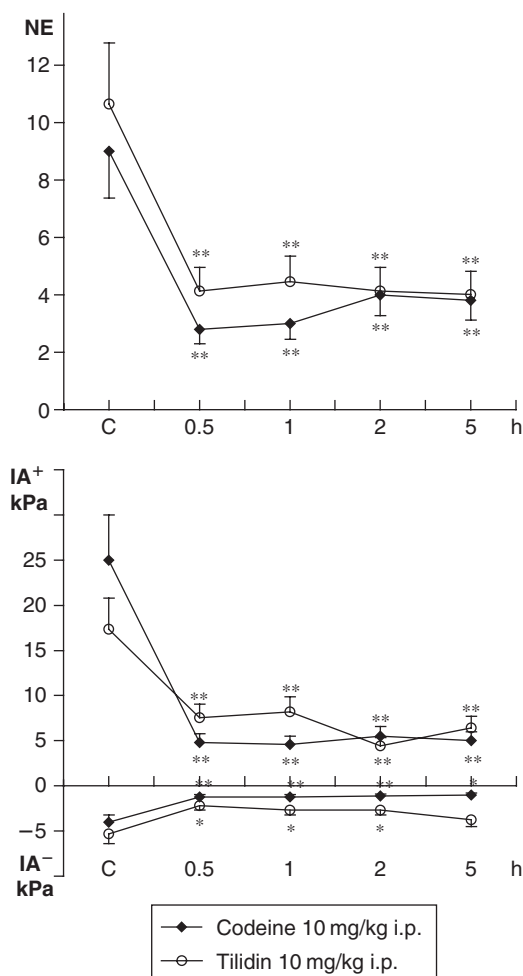


Fig. 7. Antitussive effect of tilidin compared to codeine. NE – number of cough efforts after mechanical stimulation of tracheobronchial area of the airways, IA⁺ – intensity of cough attack in expirium, IA⁻ – intensity of cough attack in inspirium, C – control, 0.5, 1, 2, 5 h – time after administration of tested substance.

be ideal from the pharmacological point of view, but they are not selective enough. The inhalation of anesthetizing aerosols leads to desensitization of cough receptors as well as other segments of mucous membranes in the mouth, and the upper and lower parts of the respiratory system, and increases the risk of aspiration (Sevecova and Calkovska, 2002; Sevecova et al., 2002). Inhalant procaine, lidocaine and bupivacaine inhibit the cough reflex elicited by both mechanical and chemical irritation. In clinical settings, the local anesthetics are used for the elimination of cough before diagnostic procedures such as laryngoscopy, bronchoscopy, intubations, etc. In the mechanism of action of some cough-suppressing agents (benzonatate – Tessalon, dropropizine – Ditustat) a local anesthetic activity takes place apart from other properties (Nosalova and Strapkova, 1989; Korpas and Nosalova, 1991).

XII.B. Drugs affecting the propagation of cough impulses in afferent nerves

Information from cough receptors localized in the airways are spread through various branches of vagal and glossopharyngeal nerves. In cough evoked by unilateral irritation due to bronchial tumor it is possible in certain conditions to use lead anesthesia of vagal nerve stem.

XII.C. Drugs modulating the central coordination of cough reflex

The drugs that suppress the cough reflex by central mechanism are listed in Table 4. In the past, alkaloids and opium derivatives were the only group of drugs the physicians used for cough suppression. The antitussive activity of these agents is associated with their ability to lower the sensitivity of the cough center to nerve impulses coming from airways receptors (Fox, 1996b). Although this group can suppress the cough very potently (Figure 2), the contemporary trend worldwide is to limit their use as they also suppress the breathing center. This unwanted effect occurs especially in children. The other negative property is the diminished activity of bronchial glands, leading to an increase in phlegm viscosity and worsening of expectoration. A very important adverse effect is their ability to induce drug dependence.

Dextromethorphan represents the most important member of the group of synthetic morphine derivatives (Rhinotussal, Romilar), which show, according to our results, excellent antitussive activity (Strapkova et al., 1987). They do not induce drug dependence and their significantly suppressive effect on cough does not suppress the breathing center. Adverse effects, which occur in less than 1% of people, include drowsiness, dizziness, nausea, constipation and abdominal discomfort. Dextromethorphan is contraindicated in a person taking monoamine oxidase inhibitors (MAOI).

Another drug with central cough-suppressing effect is clobutinol (Silomat). Clobutinol does not have the addictive properties of codeine and it does not suppress the breathing center: rather, stimulates it. It is suitable for cough therapy to treat hemoptysis and severe pertussis and to conduct endoscopic procedures in respiratory system.

XII.D. Drugs acting at the level of efferent nerves

Efferent nerves conduct the impulses activating the expiratory skeletal musculature, laryngeal muscles, tracheobronchial smooth muscles and secreting apparatus. Cough can be suppressed by pharmacodynamic elimination of any part. The most significant suppression can be achieved by myorelaxants, which block the expiratory muscles. However, this method is not recommended because of its serious adverse effects. Some authors include ganglioplegics, mostly hexamethonium, in this group.

XII.E. Drugs affecting the effectors

Lately, bronchodilators have started to be used in the therapy of cough. Bronchodilating action is one effect of dropropizine (Ditustat), L-dropropizine (Levopront) and butamirate citrate (Sinecod), which suppress cough by relaxing the bronchial muscles and facilitating the expectoration. In addition to their bronchospasmolytic and secretomotoric activity, these drugs also have an anti-inflammatory effect. The stimulatory effect on the breathing center and the absence of drug dependence are of great importance (Nosalova et al., 1984; Korpas and Nosalova, 1991).

Another agent with significant bronchodilating activity is pentoxyverine (Sedotussin), which acts at the level of the peripheral parasympathetic nerve endings, similar to atropine.

XII.F. Mucoactive substances

Mucoactive substances are representatives of a specific group of drugs. They do not affect the cough receptors directly, but modify the physical and chemical properties of bronchial secretions in order to facilitate their motion in an oral direction (Rubin, 2003). Their therapeutic goal is to change dry, irritant and nonproductive cough to so-called productive cough with nonirritating expectoration (Strapkova, 2000). The effects of *Sirupus althaeae* (Nosalova et al., 1992, 1993) and other herbal substances, mentioned in Chapter 7 are especially beneficial. This group of drugs (Table 5) is used in clinical conditions for the treatment of cough with hypersecretion phenomenon (Braga et al., 1989).

XII.G. Demulcerative and hydrating drugs

Demulcerative and hydrating drugs are water-soluble substances with high molecular weight, but without any pharmacological activity. Despite this they are used for the treatment of upper airway inflammations, sore throat and other diseases associated with dryness in mouth, irritation in throat and cough. The representatives of this group are glycerin, liquorices, synthetic cellulose derivatives, sugar syrup, honey, etc. The goal of this kind of treatment is to create a defense layer protecting the mucous membranes from other irritant stimuli (Braga et al., 1989; Franova et al., 1998). Various plants are rich in this kind of agents and are discussed in Chapter 7.

Table 5

Classification of mucoactive drugs according to direct or indirect effects on bronchial secretions (by Braga and Allegra, 1989)

Mucoactive substances		
Directly acting	Drugs destroying mucous polymers	Thiols – <i>N</i> -acetylcystein (ACC, Broncholsin, L-Cimexyl, Solmucol), Mesna (Mistabron) Enzymes—Trypsin, chymotrypsin, streptokinase other – Urea, citric acid, Hypertonic salt solutions, Anorganic iodides
Indirectly acting	Drugs modifying mucin biochemistry and mucus secretion	Carbocysteine (Fenorin, Mucopront, Mucodyn) Bromhexine (Bisolvon, Bromhexin, Flegamina, Paxirasol)
	Drugs modifying the adhesiveness of the gel layer	Ambroxol (Ambrobene, Ambrosan, Bronchopront, Mucosolvan) Tyloxapol (Tacholiquin)
	Drugs modifying the sol layer and hydration	Water Sodium salts Potassium salts
	Volatile inhalants and balsams	Terpenes Phenol derivatives
	Drugs stimulating gastropulmonary reflex	Ammonium chloride Guaifenesin (Guajacuran) Ipecacuanha Sodium citrate
	Drugs modifying bronchial glands activity	Sympathomimetics Parasympathomimetics Corticosteroids Antihistamines

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