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A Semantic Approach to Chronic Cough

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ABSTRACT

During the last decade, progress has been made with certainty in the knowledge of the pathophysiology of chronic cough and, as a consequence, a new vocabulary has been generated. This article aims to relate the vocabulary to old and new pathophysiological concepts and clinical symptomatology so that we can better understand current advances and the information that will arrive in the coming years. We intend to relate the linguistic forms with non-linguistic concepts and mental representations to facilitate the understanding of the information.

Keywords: Chronic cough. Hypersensitivity syndrome. Terminology.

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INTRODUCTION

Chronic cough is a common complaint worldwide and one of the most frequent concerns prompting patients to seek a physician consultation. It is one of the most common symptoms presented to respiratory physicians. It was found to cause 29.5 million doctor visits per year in the United States[1] and 1.38 million general practitioner visits per year in Australia[2].

The overall global prevalence of chronic cough is approximately 10%[3]. One of the problems to calculate the prevalence is its definition as well as its denomination. There is a large variety of terms in clinical use to describe cough. Classically, the description or definition has been based on symptom duration, and the characteristics of the cough, in particular whether "dry" or "wet"/"productive". Other terms such as "refractory", "unexplained" or "idiopathic" have been used interchangeably to describe persistent cough without an evident cause that explains or justifies it. In addition, most studies (82%) do not evaluate cough as a primary outcome, but rather as a respiratory symptom[3]. Behind the word cough, there are hidden many and varied concepts, which we will try to explore in more detail.

CLASSIFICATION OF COUGH

Cough can be classified according to different criteria. The two most frequent criteria are cough duration and its physiology/pathophysiology. Originally, coughing was considered a protective airway reflex, and in many cases it still is. It was also regarded as a symptom of the respiratory tract, as we have already mentioned above, the most frequent symptom. But it was not until relatively recently, due to the result of the studies developed on cough receptors, that cough began to be regarded as a disease in its own right. Cough as a disease is linked to the description of the so-called laryngeal hypersensitivity syndrome. If the classification is made according to duration, acute cough is that which lasts less than three weeks, subacute cough between three and eight weeks and chronic cough more than eight weeks (Fig. 1).

MECHANISM OF COUGH

Cough itself represents a temporary reconfiguration in the normal pattern of breathing[4]. In its purest form, coughing is a three-stage event that occurs after stimulation of peripheral receptors: an inspiratory effort (inspiratory phase), followed by a forced expiratory effort against a closed glottis (compressive phase) followed by opening of the glottis and a rapid expiratory airflow (expulsive phase)[4] (Fig. 2).

PHYSIOLOGY OF COUGH REFLEX

As in all reflexes occurring in the organism, the cough reflex has two basic components. First, there must be stimulation of the peripheral receptor that leads to depolarization of the membrane of the neuron that carries the information to the cough centre located in the medulla (afferent pathway). There, it will synapse with a neuron that will send an order (efferent pathway) to the peripheral musculature that will provoke a muscular contraction, and therefore the completion of the reflex. We will now discuss in more detail the different phases of the neurophysiology of cough.

Types of cough

According to duration	According to psysiology/pathophysiology
Acute cough < 3 weeks	Cough as a vital protective reflex preventing aspiration
Subacute cough 3-8 weeks	Cough as a symptom of a disease
Chronic cough > 8 weeks	Cough as a disease itself

Figure 1. Types of cough according to its duration and pathophysiology.

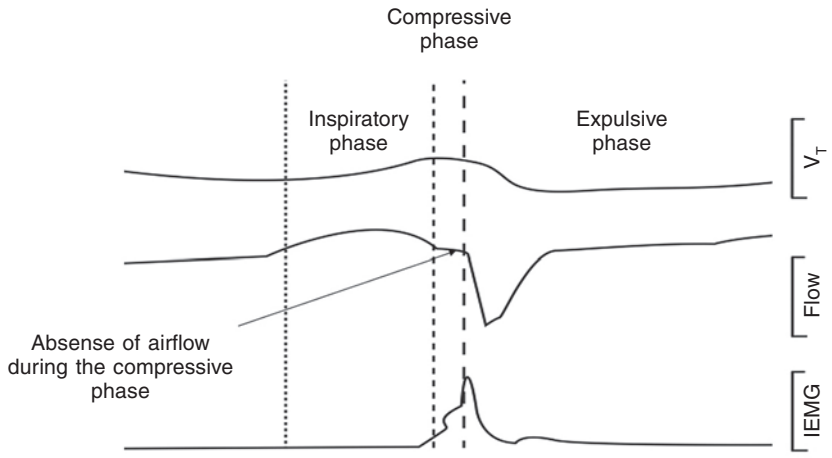

Figure 2. Different phases of cough. The figure shows a single cough. Traces are tidal volume (V_T), airflow and the integrated electromyographic activity of the right abdominal oblique muscle (IEMG). Note that there is absence of airflow during the compressive phase *(modified from Widdicombe and Fontana[5]).*

Afferent phase of cough reflex

The peripheral receptors

Each cough occurs through the stimulation of a complex reflex arc. Cough is initiated following activation of sensory nerves in the upper and lower respiratory tract. Sensory nerve receptors are tailored to detect changes in the physical and chemical environment, and if required, elicit protective reflex events such as cough.

Initially, much research was done on a family of irritable receptors called Transient Potential

Receptor (TPR). These receptors are located on nerve endings and are exposed to stimuli. Within this family, the TRPV1 receptor that can be stimulated by capsaicin (a substance extracted from chili peppers that causes coughing) and pain depending on the location of this nociceptive receptor was found to be increased in patients with chronic cough[6]. More interesting, however, was the cold receptor TRPA1, which is found in many areas and binds to many environmental irritants that patients complain about. The hypothesis of overactivation of this receptor in cough hypersensitivity is plausible, but research showed that this receptor blockade did not reduce cough. Posteriorly, other receptors were investigated. The P2X3 receptors are ligand-gated ion channels that respond to adenosine triphosphate (ATP) and are almost exclusively localized on C-fiber sensory neurons, which innervate the upper and lower airways and are the main nerve fibers responsible for cough. ATP is released by damaged, stressed, and inflamed tissues. The action of ATP at sensory neurons in the periphery and spinal cord contributes to neural excitability and may cause hyperresponsiveness through binding to P2X3-containing receptors and stimulating of C-fiber neurons[7-8]. P2X3 receptors are ATP-activated ion channels that consist of 3 subunits; these may be identical P2X3 subunits or contain a single P2X2 subunit, known as P2X2/3 channels. Antagonism of P2X3-containing receptors was then predicted to normalize sensory neuron sensitivity, based on data from P2X3 knock-out mice and the effects of small interfering RNA knock-down and pharmacological antagonists[9-11].

ATP and P2X3-containing receptors have been shown to be involved in airways sensitization, and their involvement provided a rationale for P2X3 antagonism in the treatment of cough.

The interference with taste perception

The P2X3 receptors are also involved in taste. Taste buds are unique among the special sensory end organs in utilizing ATP as the primary transmitter that links activation of receptor cells to excitation of afferent nerve fibers. Taste stimuli evoke the release of ATP from taste receptor cells[12-15] which then activates gustatory afferent fibers expressing the ionotropic purinoceptors composed of P2X2 and/or P2X3 subunits. Evidence for the essential role of ATP in taste function is based largely on recordings from mice lacking both P2X2 and P2X3 subunits. These mice lack gustatory nerve responses to all taste stimuli[16] which suggests that all taste qualities require functional homotrimeric P2X2, P2X3 and/or heterotrimeric P2X2/3 receptors to communicate with nerve fibers. The purinoceptor subtype P2X3 is an ATP-gated ion channel primarily expressed in small-diameter primary afferent fibers (Aδ and C), which are associated with sensory perception and transmission. This receptor has been shown to have significant involvement in the cough reflex. There are two types of P2X3 receptor: the homotrimer (P2X3) and the heterotrimer (P2X2/3). P2X2/3 receptors have been implicated in taste disturbance. The selectivity for P2X3 over P2X2/3 channels can help to explain the degree of taste disturbances caused by receptor antagonists[17].

Specific blockade of P2X3 receptors is not expected to result in marked impairment in taste perception owing to the more prominent role of P2X2/3 in taste perception and transmission,

the lower proportion of P2X3 receptors compared with P2X2 receptors in taste buds, and possible channel redundancies involved in the transduction of taste bud responses[18,19]. This was also suggested by a recent study of another P2X3 selective antagonist (eliapixant)[20]. Table 1 shows a glossary of terms regarding the different changes in taste perception.

Table 1. Glossary of terms regarding taste disturbances

Term	Definition
Ageusia	Loss of sense of taste
Dysgeusia	A taste disorder. People with the condition feel that all foods taste sour, sweet, bitter or metallic
Hypergeusia	Taste disorder where the sense is abnormally heightened
Hypogeusia	Reduced ability to taste sweet, sour, bitter, or salty things

The neurosensory fibers

Two main pathways have been identified. The jugular vagal C-fibers, which are nonmyelinated fibers in which the stimuli evoking action potential discharge are capsaicin and endogenous inflammatory agents (bradykinin and prostaglandin E2). These fibers have a chemo-sensitive function. The other pathway is the nodose vagal afferent Aδ fibers which are myelinated fibers and respond to mechanical stimulation and osmotic solutions (citric acid) but not to inflammatory stimuli. These fibers have basically a mechano-sensitive function.

Mapping the brainstem terminations of tracheal and laryngeal afferent fibers using neurovirulent viruses showed that afferent neurons terminate in two brainstem nuclei, the nucleus of the solitary tract (nTS) and the trigeminal/paratrigeminal nuclei (Pa5)[21].

THE CENTRAL NUCLEI

In the human brainstem, the solitary nucleus, also called nucleus of the solitary tract, nucleus solitarius, and nucleus tractus solitarii (SN or NTS), is a series of purely sensory nuclei (clusters of nerve cell bodies) forming a vertical column of grey matter embedded in the medulla oblongata. Through the center of the SN runs the solitary tract, a white bundle of nerve fibers, including fibers from the facial, glossopharyngeal and vagus nerves, that innervate the SN. The SN projects to, among other regions, the reticular formation, parasympathetic preganglionic neurons, hypothalamus and thalamus, forming circuits that contribute to autonomic regulation. Cells along the length of the SN are arranged roughly in accordance with function; for instance, cells involved in taste are located in the rostral part, while those receiving information from cardio-respiratory and gastrointestinal processes are found in the caudal part.

Neurons that innervate the nervous system mediate the gag reflex, the carotid sinus reflex, the aortic reflex, the cough reflex, the baroreceptor and chemoreceptor reflexes and several respiratory reflexes.

The upper central nervous system facilitation

Coughing can occur as a reflex action, requiring an external stimulus, it is involuntary

(absence of control by the individual) or it can occur voluntarily, in which case it does not require external stimuli and occurs as a consequence of a conscious decision by the individual. Figure 3 describes the different stages and regulatory structures that intervene in the regulation of cough. Vagal sensory neurons from the nodose (pale green) and jugular (dark green) ganglia that project to the airways and lungs have distinct central termination patterns in the brainstem. Nodose neurons have well-defined terminations within the nucleus of the solitary tract (nTS), while jugular neurons have recently been shown to terminate in the paratrigeminal nucleus (Pa5). These brainstem nuclei give rise to both local projections within the brainstem to the respiratory central pattern generator (CGP), presumably responsible for reflex coughing, as well as ascending projections to the higher brain, needed for conscious and behavioural elements of cough[23].

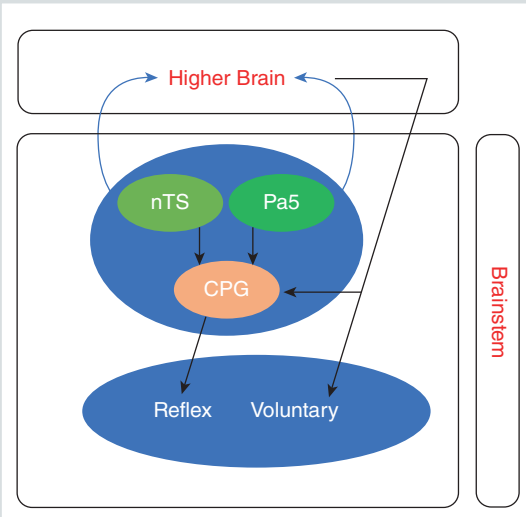

Figure 3. Different stages and regulatory structures that intervene in the regulation of cough *(modified from Keller et al.)*[22].
CPG: central pattern generator; nTs: nucleus of the solitary tract; Pa5: paratrigeminal nucleus.

THE EFFERENT PHASE OF COUGH REFLEX

This phase follows the usual physiological response of the orders coming out of the central nervous system. At this level it does not deserve further comment.

INTEGRATION OF THE COUGHING PROCESS AND PLACES OF THERAPEUTIC ACTION

This has been and continues to be a transcendental aspect since it conditions not only the etiology but also the etiopathogenesis of cough. Classically, it was considered that chronic cough could be caused by a disease related to one of the three main groups (gastroesophageal reflux disease, post-nasal drip and airway diseases)[24]. Recently, the term cough hypersensitivity syndrome has been proposed to describe a group of patients with chronic cough and similar clinical characteristics. These similar clinical characteristics include irritation in the throat or upper chest, cough triggered by stimuli that do not normally cause cough, increased cough sensitivity to inhaled stimuli, and cough paroxysms. A potential biologic explanation for cough hypersensitivity syndrome suggests an underlying sensory neuropathy characterized by sensory nerve hypersensitization. Prior Phase 2 data already supported the role of P2X3 antagonism in the treatment of patients with refractory or unexplained chronic cough.

TERMINOLOGY

In this section we will comment on the most ancient and modern vocabulary used in the field of chronic cough.

Classic terminology

As said before, it was considered that cough could be caused by three major groups of pathologies. The correct etiological treatment, however, did not always solve the clinical problem of chronic cough. The term refractory cough was coined for this group of patients. In another group of patients with chronic cough, there was no underlying cause that could ultimately explain this cough. These patients were diagnosed with unexplained chronic cough (Fig. 4). Table 2 proposes definitions for these terms.

New terminology

A new (possibly revolutionary) concept has been recently introduced, that involves the laryngeal hypersensitivity. The terms "idiopathic", "refractory" or "unexplained" cough (ICC/RCC/UCC) could be considered archaic, as a new concept could explain them all.

Several terms have been introduced, such as "cough hypersensitivity" and "laryngeal hypersensitivity". These terms are important because they are intended to address some of the limitations of the unexplained/refractory cough terms, and to better describe the underlying pathophysiology of chronic cough. McGarvey et al.[27] believe that the term "cough hypersensitivity syndrome" (CHS) which was first proposed by a working group of the European Respiratory Society is of particular clinical relevance as it delves into a new pathophysiological process with its own clinical features.

The most recent literature reflects the belief that the term CHS as a concept underlying cough, whether explained, unexplained or refractory, is fundamental to the development of new drugs in this field.

As a result of advances in the understanding of the pathophysiology of the disease, the terms ICC/UCC/RCC are now imprecise because patients with these conditions may respond to new therapeutic approaches. The term CHS and its related symptomatic patterns (alotusia, hypertusia, paresthesia, Table 3) are potentially useful terms.

FUTURE INVESTIGATIONS, FUTURE TREATMENTS

Research in the field of chronic cough has encountered many difficulties, resulting in compounds that have shown promise in preclinical models of cough while showing disappointing results in clinical trials. This calls into question whether preclinical animal and cellular studies adequately reflect the physiopathology of chronic cough as it occurs in humans. The fact that rats and mice do not cough, for example, and guinea pigs have characteristics leading to cough that may not be critical in humans, suggests that great care must be taken when using these models to investigate cough mechanisms in humans. In many cases, translation to clinical utility remains a challenge.

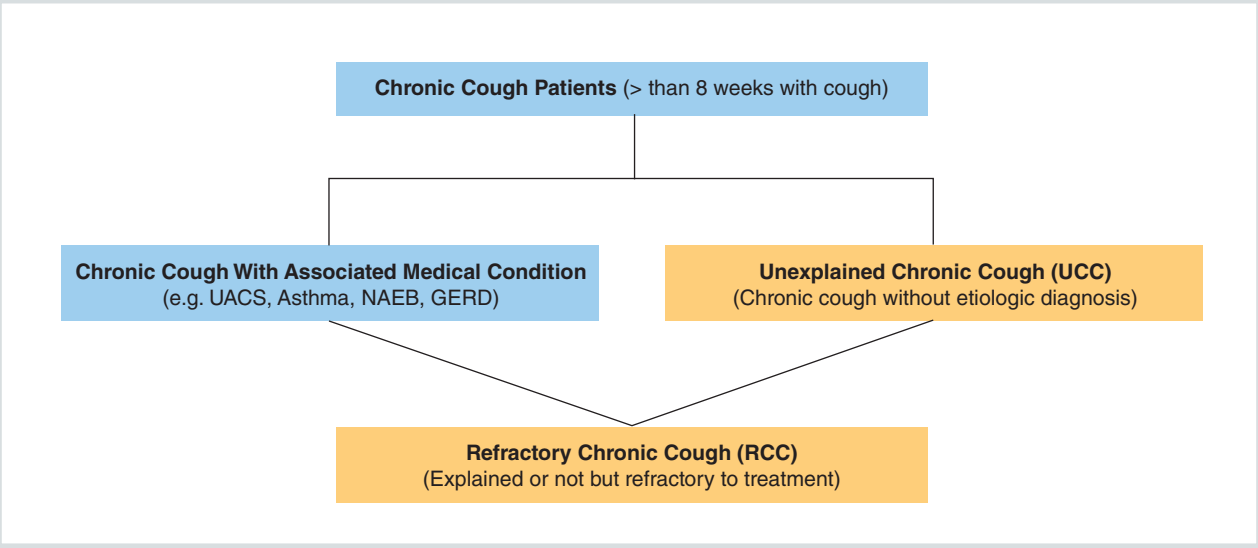

Figure 4. Concepts of refractory and unexplained chronic cough.
GERD: gastroesophageal reflux disease; AEB, nonasthmatic eosinophilic bronchitis; UACS: upper airway cough syndrome.

Table 2. Definitions regarding refractory and unexplained chronic cough

Term	Definition
Refractory chronic cough	This term applies to those patients who have been diagnosed with conditions that are suspected to cause chronic cough (i.e., asthma, GERD, UACS, or non-eosinophilic bronchitis)[25,26] in which cough persists despite correct etiological treatment
Unexplained chronic cough	This term applies to patients with chronic cough in whom an underlying aetiology cannot be identified despite a thorough diagnostic work-up[25,26]

GERD: gastroesophageal reflux disease; UACS: upper airway cough syndrome.

Table 3. Glossary of terms related to the cough hypersensitivity syndrome

Term	Definition
Allotussia	Cough triggered by stimuli that act at lower thresholds than usual, so that cough is generated in individuals who present this phenomenon but are insufficient to trigger cough in healthy individuals
Hypertussia	Excessive response to stimuli that naturally generate coughing in healthy individuals
Urge to cough	Also known as "laryngeal paresthesia", it is an itching sensation in the airways that does not disappear when coughing

Therefore, we believe it is relevant to take into account in future research both the development of new experimental models and the characteristics of the pathophysiology of cough that we have presented in this article, which allow us to better interpret the level of intervention on which we are working.

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