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COUGH TRIGGERED BY VIRAL INFECTION

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ABSTRACT

Cough is a reflex mechanism that is common in many infections, especially those affecting the respiratory tract. Cough is a nociceptive reflex that can be caused by viral infections, such as colds or the flu. Bacteria can also be a cause of cough, as occurs in pneumonia or bacterial bronchitis. Cough can develop as dry cough (caused by viral infections), productive cough with phlegm (typical of bronchitis and pneumonia), and persistent cough due to prolonged inflammation. Cough receptors are divided into mechanoreceptors which are sensitive to mechanical stimuli such as bronchospasm, edema, mucus, and foreign bodies, and chemoreceptors which are mainly sensitive to chemical stimuli including inflammatory cytokines, gases, and smoke. Both mechanoreceptors and chemoreceptors bind irritants of the myelin type, and they are sensitive to capsaicin. Respiratory syncytial virus (RSV) is a virus that affects the respiratory system and causes a persistent cough that can range from mild to severe. RSV primarily infects the lungs and airways, where it causes inflammation of the bronchioles and stimulates mucus production. The cough may cause serious symptoms such as high fever, bluish skin due to low oxygen levels, and short or long apnea. Various agents can cause cough by activating molecular and biochemical mechanisms, including viruses which can activate the immune and inflammatory response with the irritation of the airways and nerve stimulation.

KEYWORDS: *Cough, virus, infection, receptor, bronchiolitis, respiratory syncytial virus*

INTRODUCTION

Cough is a nociceptive reflex mechanism controlled by the brain stem in the "cough center" in response to sensory afferent stimuli. Motor efferent stimuli produce cough by forced expectoration with a closed glottis (1). Cough aims to remove noxa that accidentally encounters the respiratory tree (2). It is one of the most important defence mechanisms of the body and has been referred to as the "watchdog of the respiratory system" (3).

The cough reflex is stimulated by receptors that are sensitive to foreign substances such as infectious, mechanical, and chemical stimuli. These receptors are present in the epithelium of the main airways, the posterior part of the trachea, the pharynx, cornea, the proximal airways, the paranasal sinuses, the stomach, the external auditory canal, the pleura, and the pericardium; they are absent in the alveoli (Fig.1).

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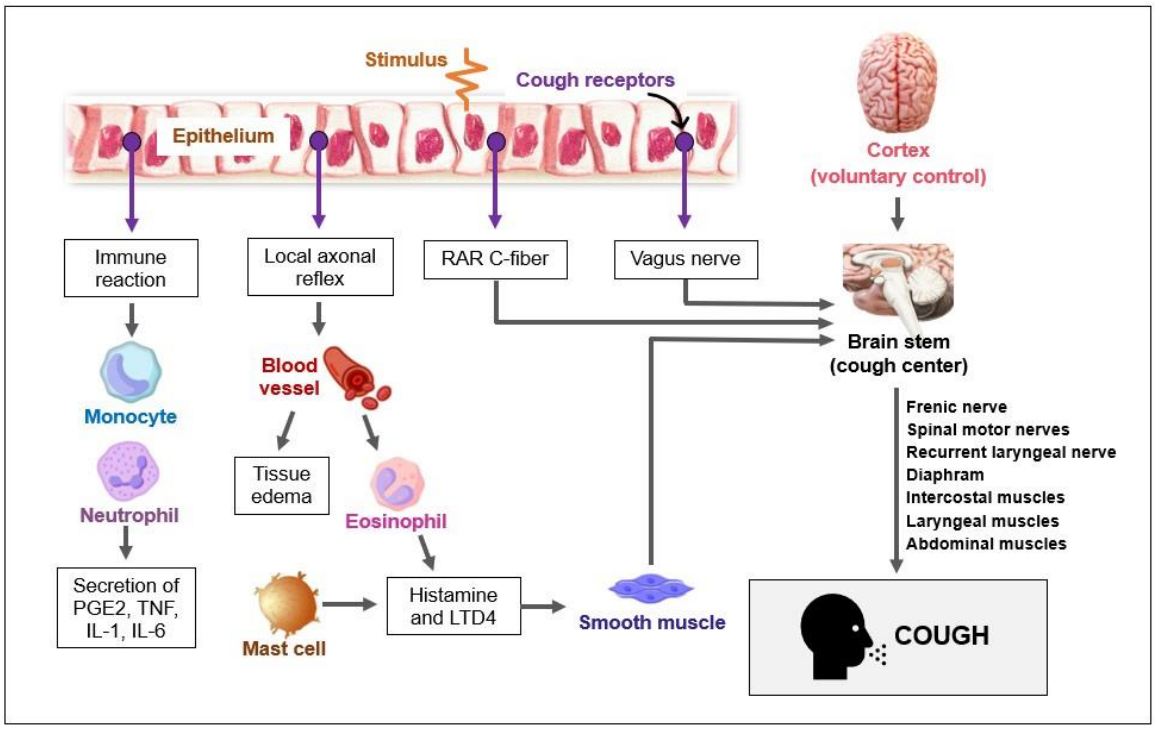

Fig. 1. *Cough receptors are activated in response to infectious, mechanical, and chemical stimuli, and cause an immune reaction that results in the secretion of inflammatory substances and a local axonal reflex that results in tissue edema and the release of histamine and LTD4 which affects smooth muscle cells to produce cough. Cough receptors also stimulate RAR C-fibers and the vagus nerve which participate in the activation of cough through the brain stem.*

Cough receptors include mechanoreceptors that are sensitive to mechanical stimuli such as bronchospasm, edema, mucus, foreign bodies, and chemoreceptors that are mainly sensitive to chemical stimuli including inflammatory cytokines, gases, and smoke (4). The density of mechanoreceptors is highest in the proximal walls of the airways such as the larynx and trachea. Chemoreceptors, on the other hand, are located primarily at the base of the airways (5). Receptors can be further divided into rapidly and slowly adapting irritant receptors of the myelin type, which includes both mechanoreceptors and chemoreceptors, and receptors sensitive to capsaicin which only include chemoreceptors (6). The latter are in the trachea and bronchi and are able to cause muscle contraction, vasodilation, and mucus secretion through an accentuation of the cough reflex.

Some individuals have a higher distribution of chemoreceptors, particularly capsaicin-sensitive receptors (7). These individuals have a greater frequency and duration of coughing episodes.

Once activated, cough receptors transmit impulses from the branches of the internal laryngeal nerve to the superior laryngeal and vagus nerves (8). Some afferents are transmitted through the glossopharyngeal and trigeminal nerves.

DISCUSSION

Cough is defined as chronic when it last for more than three weeks, and as acute when it lasts less than three weeks weeks (9,10). It is generally caused by viral infections and sometimes, accompanied by fever (11). The incidence of acute cough is high in the first years of life, especially in school-aged children, who can contract up to 6-8 viral infections of the upper respiratory tract each year.

Cough is characterized by sudden, intense, and annoying attacks, with the emission of mucus (12). In most cases of acute cough, a careful anamnesis and physical examination are sufficient for the diagnosis. Since most acute cough episodes have a viral etiology, specific therapy is almost never necessary (13). Cleaning the nasal cavities with saline solution and maintaining a raised decubitus during sleep are useful.

The areas of the central nervous system (CNS) responsible for controlling the cough reflex are in the brainstem (14). The efferent neural pathway starts from the cerebral cortex, passes through the nuclei of the brainstem tract, continues with the vagus nerve, the superior laryngeal nerve to the glottis, and is transmitted to the external intercostal respiratory muscles and diaphragm. Through the capsoid-sensitive C-fibers, the cough reflex is linked to the production of mucus in the submucosal glands and goblet cells, contributing to the establishment of a further defence mechanism,

since the action of the mucociliary clearance contributes to the removal of foreign substances from the mucosa of the respiratory tract (15).

Coughing is regulated by a complex muscular mechanism that can be divided into three phases. The first, called the inspiratory phase, involves the massive entry of air into the lung parenchyma (16). The diaphragm and the external intercostal muscles contract, creating a negative intrapulmonary pressure, which allows, together with the contraction of the abductor muscles of the arytenoid cartilages, the forced inspiration of air. The second phase, called the compressive phase, entails the closure of the glottis for about 2 tenths of a second (17). At the same time, there is a strong contraction of the abdominal muscles and the expiratory muscles, with an increase in air pressure inside the lungs up to 300 mm/Hg. The expulsive phase consists of the opening of the glottis, with the emission of air at more than 160 km/h (18). During a coughing fit, the compressive and expulsive phases can be repeated in succession, even without an inspiratory phase.

Chronic cough can be caused by various conditions that vary with the age of the patient. Cough may appear after an infection and is called post-infectious cough. This is caused by viral infections and is slow to resolve. The mechanism is related to persistent inflammation of the airways with transient hyperreactivity of cough receptors that continues after the elimination of the viruses (19). Cough can occur a few days after an episode of fever or concomitant with it and generally lasts from 3 to 8 weeks. An individual with post-infectious cough typically has a history of fever or cold episodes in the days preceding the cough. The specific infection causing the cough remains unknown in most cases. In the absence of a documented bacterial infection, there is no need for specific treatment. The recent guidelines of the American College of Chest Physicians recommend the use of inhaled ipratropium bromide as a supportive drug for the improvement of symptoms (20).

Viral infections can cause bronchiolitis, acute inflammation which is associated with bronchiolar obstruction and characterized by dyspnoea, tachypnoea, and wheezing (21). This is the most common lower airway disease in the pediatric population and is responsible for the majority of hospitalizations in the first twelve months of life. The diagnosis involves the use of classical and molecular diagnostic techniques and it has been shown that 97% of cases of bronchiolitis are of viral etiology, and that in 24% of cases of immunocompetent patients, more than one infectious agent is present (22). The main etiological agent is the respiratory syncytial virus (RSV), which is responsible for 45-75% of bronchiolitis cases in children, especially those that occur in epidemic form. Following RSV is metapneumovirus, parainfluenza virus types 1, 2, and 3, bocavirus, adenoviruses, and enteroviruses (23). More rarely, influenza viruses, echoviruses, rhinoviruses, or bacteria such as *Mycoplasma pneumoniae*, *Bordetella pertursis*, and *Simkania negevensis* are responsible.

Bronchiolitis is a highly contagious infection and is transmitted both by direct contact with nasal secretions of infected individuals and through direct contact by infected hands (21). The causative virus often survives at room temperature, for eight hours on the skin, and for about 6 hours on various surfaces. It is usually contracted in the community or through contact with an infected family member. Transmission occurs by elimination of the virus two days before the onset of symptoms and continues for about a week after their resolution. The virus prefers the winter months and early spring, sometimes manifesting itself with small epidemics in communities. According to estimates provided by the World Health Organization (WHO), 150 million new cases of bronchiolitis are observed each year around the world, of which 7-13% represent one of the categories at risk of developing severe forms which could require hospitalization (24).

RSV is a virus that affects the respiratory system, especially in young children and older adults (21). One of the hallmark symptoms of RSV is a persistent cough, which can range from mild to severe. RSV primarily infects the lungs and airways, causing inflammation of the bronchioles and stimulating the production and accumulation of mucus that causes coughing. Cough is a protective reflex to eliminate pathogens, including RSV, from the respiratory tract (25). Coughing can last for several weeks, even after other symptoms have subsided, and is often accompanied by mucus that is difficult to clear. Serious symptoms that can occur with a cough include high fever, bluish skin or lips due to low oxygen, and apnea with pauses in breathing that may be short or long (26). Treatments include hydration to help thin the mucus, saline drops or sprays, and bronchodilators which help open the airways. Most often, cough caused by RSV resolves spontaneously, but it is essential to monitor for any complications such as bronchiolitis or pneumonia.

CONCLUSIONS

In the airways, viral infections can cause cough by activating molecular and biochemical mechanisms. Cough involves a cascade of events that begin with the entry of the virus, activation of the immune response, and nerve stimulation. Coughing causes irritation of the airways, increased mucus production, and inflammation, and can lead to more severe symptoms such as high fever, low oxygen levels, and apnea.

Conflict of interest

The authors declare that they have no conflict of interest.

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