Novel approach to chronic cough

NAUJAS POŽIŪRIS Į LĖTINĮ KOSULĮ

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Summary. Cough is the most common symptom for which people seek medical advice. A multitude of reasons can cause it. In clinical practice, a new term "Cough hypersensitivity syndrome" was proposed, which defines unaccountable reasons for cough and different groups of patients with chronic cough. Adenosine triphosphate (ATP) as a driver of chronic cough is the most important target in nowadays clinical trials. Extracellular ATP activates P2X purinoreceptor 3 (P2X3) receptor channels, which are expressed in sensory neurons. New treatment methods that block P2X3 receptors are being developed.
Keywords: chronic cough, cough hypersensitivity syndrome, adenosine triphosphate, novel treatment options.
Santrauka. Lėtinis kosulys yra dažniausias skundas, dėl kurio pacientai kreipiasi į gydytojus. Kosulį sukelia įvairios priežastys ir sutrikimai. Klinikinėje praktikoje vartojamas naujas terminas „Kosulio hiperjautrumo sindromas", kuris apima neaiškos kilmės kosulio priežastis bei skirtingas pacientų, besiskundžiančių lėtiniu kosuliu, grupes. Adenozino trifosfatas (ATP), kaip vienas pagrindinių kosulį sukeliančių veiksnių, šiuo metu yra dažniausiai klinikiniuose tyrimuose tiriama cheminė medžiaga. ATP aktyvuoja P2X purino receptoriaus 3 (P2X3) jonų kanalus, kurie yra išreikšti jutiminiuose neuronuose. Nauji gydymo metodai, blokuojantys P2X3 receptorius, yra daug žadantys gydant lėtinį kosulį.
Reikšminiai žodžiai**:** lėtinis kosulys, kosulio hiperjautrumo sindromas, adenozino trifosfatas, naujos gydymo galimybės.

INTRODUCTION

Cough is the most frequent symptom and reason, why patients seek medical assistance. Doctors usually deal with acute cough in their daily practice, which typically is the outcome of getting cold. Chronic cough, however, is still shrouded in mystery. It is defined as cough, lasting more than 8 weeks [1]. Cough affects people's health differently. In acute cough cases, health is disrupted temporally. A chronic cough might be very slight, which is why patients usually do not pay attention to it and even do not seek any help, or it can be intolerable, worsening patients' quality of life. It frequently affects physical, psychological and social areas of health [2]. Patients, who suffer from chronic cough, have complaints about chest muscle pains, problems with sleep and hoarseness, as well as incontinence of urine. Less common symptoms are short loss of consciousness, vomiting, and difficulties coping with stress. The psychological aspect of the state of health is concern about untreatable diseases, like cancer or tuberculosis. Cough influences on social welfare, depending on individual factors [3].

Chronic cough is an important field in today's clinical trials. Persistent chronic cough interrupts a person's normal daily routine and is difficult to manage, so a deeper understanding of this disease pathophysiology is crucial. To discover new ways of managing chronic cough, precise pathophysiological mechanisms are being explored. One of them is adenosine triphosphate (ATP), a heavily researched substance, which might be the cause of chronic cough. Newly discovered pathophysiological mechanisms are expected to be useful in developing new antitussive therapies.

COUGH HYPERSENSITIVITY SYNDROME

There are many causes of chronic cough. In clinical practice, it is essential to recognize the condition concerning the main problem of chronic cough. Frequently they are gastroesophageal reflux disease (GORD), asthma and postnasal drip syndrome. However, there are some cases, that even after a narrow examination of the patient, it is still difficult to put chronic cough into the frames of the specific disease. In the past, a cough of unknown cause was called idiopathic. It was hypothesized that some, if not all, cases of chronic refractory/idiopathic cough may belong to a particular phenotype and share the prevalent mechanism of pathophysiology, namely cough reflex hypersensitivity [4].

Since this hypersensitivity is not limited to idiopathic cough, it was suggested that chronic cough is generally the consequence of an interaction between intrinsic cough reflex defects (i.e. hypersensitivity) and aggravating factors, such as angiotensin-converting enzyme (ACE) inhibitors, GORD, upper airway disorders, eosinophilic airway diseases and cigarette smoke/chronic obstructive pulmonary disease (COPD). A new term "cough hypersensitivity syndrome" (CHS) was proposed to name the clinical entity characterized by improved cough reflex, which includes several phenotypes depending on which aggravating factor is involved (Figure 1). However, there has been some discussion about the nature and de-

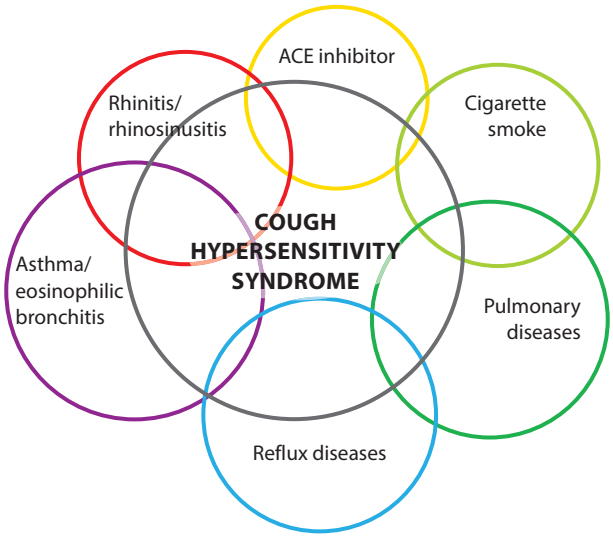

Figure 1. Cough hypersensitivity is a syndrome, which is defined as unaccountable cough reasons and different groups of patients with chronic cough [5]

ACE – angiotensin-converting enzyme inhibitors.

finition of CHS, indicating that this syndrome may stay hard to define and, therefore, to explore and to treat [5].

To address this, the European Respiratory Society (ERS) announced Task Force on cough hypersensitivity. This Task Force aimed to express international opinion on the clinical relevance of cough hypersensitivity [6].

CHS is a clinical syndrome, which involves troublesome coughing often triggered by low levels of thermal, mechanical or chemical exposure [2]. This syndrome is a new paradigm, describing unidentifiable causes of chronic cough, and involves apparently different groups of patients. CHS includes symptoms like permanent tickle or irritation feeling in the throat, hoarseness, dysphonia or obstruction of the larynx. Environmental agents, like tobacco smoke or odours, can provoke these symptoms together with a cough. Pathophysiology of hypersensitivity is still unclear, however, it is believed that it is associated with transient receptor potential (TRP) nociceptors dysfunction [5].

There are two main mechanisms of CHS: peripheral and central neural pathways (Figure 2). Airway has afferent nerve terminals, which stimulate the vagus nerve by two supplementary pathways: exogenous and endogenous [7].

Thermal, mechanical or chemical triggers mainly cause the exogenous pathway, *e.g.* solid particles of air (especially for people, living in the big, traffic-heavy cities), food (aspirated), air temperature changes (cold to warm weather, or conversely), inhaled chemicals. This pathway involves different receptors. Even though several afferent airway receptors play a significant role in the cough reflex, their role in the pathophysiology of chronic cough is still not known. The exogenous pathway involves transient receptor potential vanilloid 1 (TRPV1), transient receptor potential cation channel subfamily a member 1 (TRPA1) receptors, also P2X purinoreceptor 3 (P2X3) receptor [8].

TRPV1 is a protein encoded by TRPV1 gene in humans and is known as the capsaicin or vanilloid 1 receptor. It is believed that TRPV1 expression is increased in patients with chronic cough [8]. It is also noticed, that specific TRPV1 antagonist can successfully eliminate the cough reflex stimulated by inhaled capsaicin [9]. Despite this observation, there is a lack of evidence on TRPV1 antagonist efficacy on daily life quality changes or on reduced chronic cough frequency, and there is no significant impact of TRPV1 to the mechanisms of CHS. Mostly the same results were observed with the receptor TRPA1 [10].

ATP as a driver of chronic cough is the most important target in nowadays clinical trials. The *P2RX3* gene, which belongs to purinoreceptors for ATP, encodes P2X purinoreceptor in humans. P2X3 receptors are ATP ion – gated channels located on primary afferent neurons. ATP released from inflamed or damaged airway tissues affects primary afferent neuron P2X3 receptors, triggering depolarization and action potentials that are centrally transferred and explained as an urge to cough [11]. ATP triggers a peripheral endogenous pathway. As mentioned above, ATP interacts with P2X3. ATP directly stimulates the endogenous pathway, while experimentally inhaled tussigens cause cough mostly by the exogenous pathway [7]. For instance, both directly stimulating peripheral nerves and releasing ATP can overlap between the two paths with hypo-osmolar alternatives. The endogenous pathway may also involve peripheral mediators other than ATP [12].

Central cough pathways are associated with the vagus nerve. Vagus nerve synapses with neurons are located in a solitary nucleus within medullary "cough centre". Cough through motor efferent triggers larynx, diaphragm and intercostal muscles. Higher centres, including the cuneiform nucleus and periaqueductal gray of the midbrain, excessively stimulate the cough center in chronic cough patients [7]. At the same time, cortical impact (*e.g.* prefrontal and upper midcingulate cortex), that usually determines inhibition, is suppressed. These pathways are possibly responsible for cough hypersensitivity. Low levels of exogenous stimuli can trigger cough through peripheral nociceptors, as well as even physiological concentrations of ATP through peripheral endogenous pathway [12]. Modulation of sensory processing at the vagus nerve ganglia level may also be of high relevance. Cortical pathways involve the urge to cough and conscious sensations of coughing.

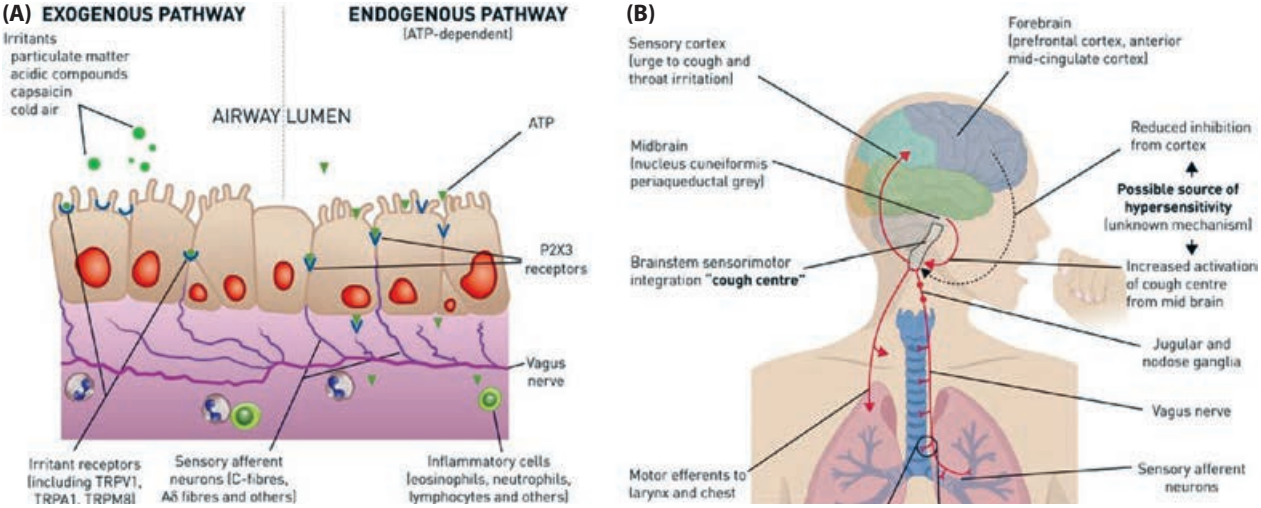

Figure 2. Cough hypersensitivity syndrome pathophysiology: a) peripheral pathway (exogenous and endogenous mechanisms); b) central neural pathway [7]

The process of hypersensitivity can be encoded both at the peripheral (cough sensory nerves) and central (brain stem and higher centres) levels. At the peripheral level of sensitization, ion channel mechanisms involving TRP cation channels and ATP are potentially altered by neuroinflammation and this alteration enhances cough sensory nerve sensibility. The central pathway is described as the presence of increased neural activity in the midbrain.

NEW RESEARCH TARGETS IN CHRONIC COUGH

ERS guidelines on the assessment of cough are based on a diagnostic approach to find the cause of chronic cough [1]. The main principle of finding it is to exclude the most common associated conditions (such as asthma, cough variant asthma, postnasal drip syndrome, eosinophilic bronchitis, GORD or upper airway cough syndrome). Hull Cough Hypersensitivity Questionnaire (HCHQ) was constructed to define and reveal the main symptoms and signs of CHS [13]. Professor A. H. Morice, together with co-authors created HCHQ, as a material, defining and revealing the main symptoms and signs of this syndrome. A questionnaire consists of 14 questions, which are rated with the score from 0 to 5. Score sum from 0 to 13 means that patients, even though they are complaining about chronic cough, do not have CHS. Score from 14 to 70-indicates CHS. In 2015^{th,} this questionnaire was translated and validated into Lithuanian language.

After the exclusion of possible chronic cough causes, there are methods used routinely in daily clinical practice. It is suggested to measure cough hypersensitivity by dividing it into two categories: subjective and objective. The subjective category has two compounds: cough related quality of life (measured by questionnaires: Leicester Cough Questionnaire, Cough – specific – Quality – of – Life Questionnaire) and cough severity (measured with cough visual analog scale (VAS)). An objective category depends on a frequency of cough (measured with cough monitors) and sensitivity of cough reflex (measured by performing tussigen inhalation challenge tests: capsaicin and citric acid) [5].

There are also new research targets used just in clinical trials. One of them, mucosal biopsies, are still the area under the research and the value of this examination is not known. Several other clinical trials discusses airway wall remodeling process when taking a biopsy, as well as bronchoalveolar lavage fluid (BAL).

Macedo et al. (2017) clinical research "Analysis of bronchial biopsies in chronic cough" examined 100 patients' mucosal biopsies: 38 patients with known chronic cough causes (asthma, GORD, postnasal drip syndrome, etc.) and 62 patients with chronic idiopathic cough (cause of cough is unknown) [14]. Patients in the former group had longer spans of cough, lower fractional exhaled nitric oxide (FeNO) levels, and more sensitive capsaicin cough response. The most important result of this study was that in all examined mucosal biopsies basement membrane thickness, goblet cell hyperplasia, submucosal gland hypertrophy with various degree of neutrophilic, eosinophilic and lymphocytic infiltration were minimally increased. This was explained as a possible injury of chronic cough on the airway mucosal and submucosal cells, causing fibrosis and chronic inflammation of the airway wall. This research provides evidence, which supports a theory that the chronic cough is the consequence of cough hypersensitivity syndrome caused by neuroinflammatory mechanism [14].

Neurogenic mechanism of chronic cough is associated with the expression of calcitonin – gene – related peptide (CGRP), which is increased in airway nerves of patients with chronic cough [15]. Another biomarker is nerve growth factor (NGF), which is released from bronchial epithelium cells, has neuroinflammatory

results, and might be important in chronic cough. NGF can have an impact on the sensory nerves of the airway through TRPV1 sensitization [4]. When compared to healthy volunteers, higher concentrations of NGF were identified in nasal secretions compared to patients with airway sensory hyperactivity to scents and chemicals, typically manifesting in the urge to cough. However, in BAL collected from patients with chronic cough, the concentration of NGF was not increased.

TGF-β is usually the most analyzed cytokine, participating in normal pulmonary morphogenesis, function, and pathogenesis of lung diseases [16]. It is believed that growth factor – TGF-β may be involved in subepithelial fibrosis and one of the neurotrophins, such as brain-derived neurotrophin (BDNF), may sensitize nociceptors and participate in angiogenesis and microvascular remodeling. Xie et al. (2009) analyzed the expression of transforming growth factor – β (TGF-β) in patients with chronic cough. This study aimed to explore the role of these mediators in the remodeling process of the airway in chronic cough patients.19 non-coughing volunteers and 13 patients with chronic idiopathic cough (non – asthmatic) participated in this study. Elevated concentrations of TGF-β were found in BAL fluid and immunohistochemical sections of the bronchial mucosa, especially in airway epithelium and airway smooth muscle cells in chronic cough patients compared to healthy volunteers. It proves that increased expression of TGF-β in the airways may be involved in the remodeling of the airway wall in chronic cough patients [17].

Arnold nerve reflex is another new research target in chronic cough patients. Dičpinigaitis et al. (2019) evaluated the prevalence of Arnold nerve reflex in subjects with or without chronic cough and its relevance to CHS [18]. Patients were assessed for the presence of the Arnold nerve reflex by insertion of a cotton-tipped applicator approximately 3–5 mm into the external auditory canal of each ear and mechanical stimulation of its circumference throughout 2–3 s. Cough occurring within 10 s of stimulation was considered to be induced by the intervention. The prevalence of the Arnold nerve reflex in adults with chronic cough is 23.3%, compared to only 2% in healthy adults without cough [18]. This higher prevalence of Arnold's nerve reflex in adult patients with chronic cough supports the concept of vagal nerve hypersensitivity to be the underlying mechanism of chronic cough, as the auricular branch of vagus nerve mediates Arnold reflex [19].

One more research target in clinical trials is functional brain imaging. Ando et al. (2016) research aimed to compare central neural responses to airway stimulation using inhaled capsaicin in healthy people and patients with cough hypersensitivity [20]. Hypersensitivity in response to inhaled capsaicin coincided with elevated neural activity in the midbrain, a region involving the nucleus cuneiformis and periaqueductal gray, compared to normal sensitivity in controls. The results of this study identified two outcomes. First, patients with CHS displayed increased neural activity (correlating with measures of sensory sensitivity) in midbrain regions not activated in controls undergoing the same experimental challenges. Second, patients with CHS displayed reduced activity in a central network involved in cough suppression, and this translated to their inability to control coughing.

Despite all these findings and discoveries, clear link between these mediators and chronic cough is not known but can point to the right direction for the implementing new therapies for this irritating symptom.

NEW POSSIBLE ANTITUSSIVE THERAPIES FOR CHRONIC COUGH

Currently, there is no effective treatment for chronic cough. The significant outcome of cough is deterioration of the quality of life, and the treatment goal is to resume a normal daily life but not to completely inhibit the cough reflex. As CHS includes various groups of this syndrome causes, first, we should treat the underlying disease. Evidently, speech therapy is

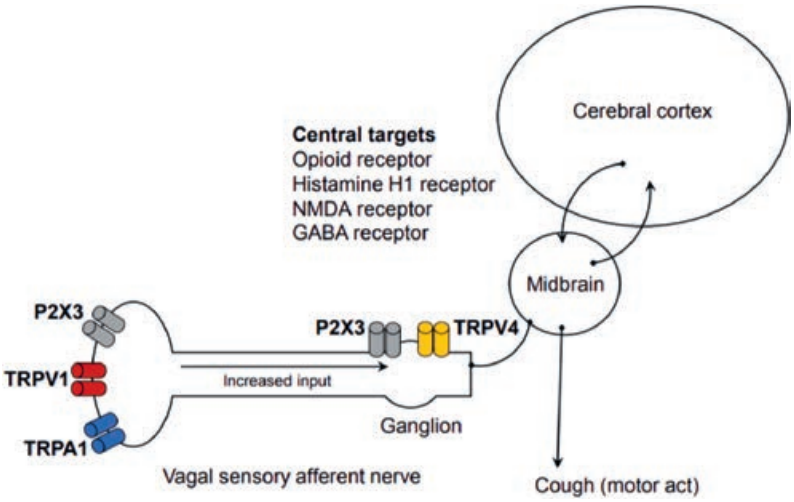

Figure 3. Possible therapeutic targets in cough hypersensitivity syndrome [5]

TRPV1, a sensory receptor for capsaicin, is expressed primarily in sensory nerve C-fibers, and its expression is increased in chronic cough patients. TRPA1, acting on vagal sensory neurons, binds to a lot of irritants, which are abundant in pollutants and cigarette smoke, and was shown to mediate cough responses. The P2X receptors are relatively specific for ATP. These latter receptors are located primarily on small afferent neurons of the C-fiber class.
GABA receptor – Gamma-aminobutyric acid receptor; NMDA receptor – N-methyl-D-aspartate receptor; P2X3 – P2X purinoreceptor 3 receptor; TRPA1 – transient receptor potential cation channel subfamily a member 1; TRPV1 – transient receptor potential vanilloid 1.

an effective intervention for refractory chronic cough [21]. Another study showed that 4 to 6 weeks of a proton-pump inhibitor alone or in combination with a prokinetic agent successfully diagnoses and treats four out of five patients with GERD-related cough [22]. However, the biggest problem is with chronic cough of unknown cause.

Considering new pathophysiology mechanism, involving ATP, one of the most examined parts of antitussive therapy is pointed to blocking P2X3 receptors (Figure 3). Phase 2 study in patients with chronic refractory cough (those whose cough does not resolve with appropriate treatment), demonstrated terrific results in reducing the frequency of daily cough when using the P2X3/P2X2 receptor antagonist – gefapixant [23]. Gefapixant is a first of its kind, non-narcotic, selective antagonist of the P2X3 receptor. Double-blind clinical trial (NCT01432730) compared data of gefapixant in chronic cough patients and healthy volunteers. This research involved 24 patients with chronic cough of unknown cause. Treatment with a high dose of gefapixant (600 mg twice daily) led to a 75% reduction in mean daytime frequency) compared to placebo [24]. Another clinical trial evaluated the effect of gefapixant on cough reflex sensitivity to evoked tussive challenge. In this phase 2, double blind trial, patients with chronic cough and healthy volunteers were randomized to single-dose gefapixant 100 mg or placebo group. Sequential inhalation challenges with ATP, citric acid, capsaicin and distilled water were performed. Objective cough frequency over 24 hours and a cough severity VAS were assessed in chronic cough patients. The ATP-evoked cough was significantly inhibited by gefapixant 100 mg [25]. This medication is currently under investigation in the 3 phase clinical trial, whose primary goal is to assess the efficacy and safety for the control of chronic cough in patients with refractory chronic cough and cough of unexplained cause [11].

Considering TRPV1 as one of a mediator of chronic cough, it was also thought to be a strong candidate for developing a novel antitussive agent [3]. However, contrary to expectations, a TRPV1 antagonist (SB-705498) failed to show any significant benefit in reducing cough frequency or improving cough-specific quality of life scores in double-blind randomized controlled trials [25].

CONCLUSION

Chronic cough remains the problem that is being intensively researched. Chronic cough hypersensitivity is a new paradigm, and this syndrome combines unexplained cough and includes different groups of patients with possible known etiologies and diseases. New pathophysiology mechanisms help us understand the underlying causes of CHS. ATP released from inflamed or damaged airway tissues affects central afferent neuron P2X3 receptors, triggering depolarization and action potentials that are centrally transferred and explained as the urge to cough. One of the most thoroughly examined part of antitussive therapy is pointed at blocking P2X3 receptors. Gefaxipant is currently under investigation in the 3 phase clinical trial, whose main goal is to assess the efficacy and safety for the control of chronic cough in patients with refractory chronic cough and cough of unexplained cause. We still need a deeper understanding of this underlying problem and more research is necessary to be done for the effective treatment for chronic cough.

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REFERENCES

1. **Morice AH, Fontana GA, Belvisi MG, Birring SS, Chung KF, Dicpinigaitis PV.** ERS guidelines on the assessment of cough. Eur Respir J. 2007; 29(6):1256–76.
2. **Morice AH.** The cough hypersensitivity syndrome: a novel paradigm for understanding cough. Lung. 2010; 188(Suppl 1):S87-90.
3. **Escamilla R, Roche N.** Cough hypersensitivity syndrome: towards a new approach to chronic cough. Eur Respir J. 2014; 44(5):1103–6.
4. **Chung KF.** Approach to chronic cough: the neuropathic basis for cough hypersensitivity syndrome. J Thorac Dis. 2014; 6(7):S699–707.
5. **Song WJ, Morice AH.** Cough Hypersensitivity Syndrome: A few more steps forward. Allergy Asthma Immunol Res. 2017; 9(5):394-402.
6. **Morice AH, Millqvist E, Belvisi G, Bieksiene K, Birring SS, Chung KF, et al.** Expert opinion on the cough hypersensitivity syndrome in respiratory medicine. Eur Respir J. 2014; 44(5):1132–48.
7. **Turner RD, Birring SS.** Chronic cough: ATP, afferent pathways and hypersensitivity. Eur Respir J. 2019; 54(1). pii: 1900889.
8. **Polverino M, Polverino F, Fasolino M, Andò F, Alfieri A, De Blasio F.** Anatomy and neuro-pathophysiology of the cough reflex. Multidiscip Respir Med. 2012; 7(1):5.
9. **Adcock JJ.** TRPV1 receptors in sensitization of cough and pain reflexes. Pulm Pharmacol Ther. 2009; 22(2):65-70.
10. **Millqvist E.** TRPV1 and TRPM8 in treatment of chronic cough. Pharmaceuticals (Basel). 2016; 9(3). pii: E45.
11. **Garceau D, Charet N.** BLU-5937: A selective P2X3 antagonist with potent anti-tussive effect and no taste alteration. Pulm Pharmacol Ther. 2019; 56:56-62.
12. **Belvisi MG, Smith JA.** ATP and cough reflex hypersensitivity: a confusion of goals? Eur Respir J. 2017; 50(1). pii: 1700579.
13. **Hull Cough Hypersensitivity Questionnaire.** International Society for the Study of Cough. Available at: http://www.issc.info/HullCoughHypersensitivityQuestionnaire.html.
14. **Macedo P, Zhanga Q, Saitoa J, Lianga Z, Folkes L, Nicholson AG, et al.** Analysis of bronchial biopsies in chronic cough. Respir Med. 2017; 127:40-4.
15. **Chang AB, Gibson PG, Ardill J, McGarvey LPA.** Calcitonin gene-related peptide relates to cough sensitivity in children with chronic cough. Eur Respir J. 2007; 30:66-72.
16. **Bartram U, Speer CP.** The role of transforming growth factor β in lung development and disease. Chest. 2004; 125(2):754–65.
17. **Xie S, Macedo P, Hew M, Nassenstein C, Lee KY, Chung KF.** Expression of transforming growth factor-β (TGF-β) in chronic idiopathic cough. Respir Res. 2009; 10:40.
18. **Dicpinigaitis PV, Enilari O, Cleven KL.** Prevalence of Arnold nerve reflex in subjects with and without chronic cough: Relevance to Cough Hypersensitivity Syndrome. Pulm Pharmacol Ther. 2019; 54:22–4.
19. **Canning BJ, Chang AB, Bolser DC.** Anatomy and neuro-

physiology of cough: CHEST guideline and expert panel report. Chest. 2014; 146 (6):1633–48.
20. **Ando A, Smallwood D, McMahon M, Irving L, Mazzone SB, Farrell MJ.** Neural correlates of cough hypersensitivity in humans: evidence for central sensitization and dysfunctional inhibitory control. Thorax. 2016; 71(4):323–9.
21. **Ryan NM, Vertigan AE, Bone S, Gibson PG.** Cough reflex sensitivity improves with speech language pathology management of refractory chronic cough. Cough. 2010; 6:5.
22. **Poe RH, Kallay MC.** Chronic cough and gastroesophageal reflux disease: experience with specific therapy for diagnosis and treatment. Chest. 2003; 123(3):679-84.
23. **Abdulqawi R, Dockry R, Hol K.** P2X3 receptor antagonist (AF-219) in refractory chronic cough: a randomized, double blind, placebo-controlled phase 2 study. Lancet. 2015; 385(9974):1198–205.
24. **Muccino D, Green S.** Update on the clinical development of gefapixant, a P2X3 receptor antagonist for the treatment of refractory chronic cough. Pulm Pharmacol Ther. 2019; 56:75–8.
25. **Khalid S, Murdoch R, Newlands A, Smart K, Kelsall A, Holt K, et al.** Transient receptor potential vanilloid 1 (TRPV1) antagonism in patients with refractory chronic cough: a double-blind randomized controlled trial. J Allergy Clin Immunol. 2014; 134(1):56-62.