Cough · 7: Current and future drugs for the treatment of chronic cough

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There are currently no effective treatments for controlling the cough response with an acceptable therapeutic ratio. However, several new mechanisms have been identified which may lead to the development of new drugs.

Chronic cough is associated with many inflammatory airways diseases such as asthma, chronic obstructive pulmonary disease (COPD), post viral infections, pulmonary fibrosis, and bronchiectasis. Indeed, it is the first and most persistent symptom of diseases such as asthma and COPD. Furthermore, it is the most common respiratory complaint for which medical attention is sought and, although UK annual sales of over the counter (OTC) cough remedies are over £0.5 billion, effective treatments for cough are very limited. In fact, a recent study has suggested that OTC medicines for acute cough cannot be recommended because there is no good evidence for their effectiveness given that, even in studies where OTC compounds showed minimal benefits, these were of doubtful clinical relevance. The identification of new therapeutic targets for the treatment of chronic cough will therefore be of immense therapeutic benefit and will greatly enhance the quality of life of patients.

CURRENT TREATMENTS

Opiates

The most effective antitussive agents are opioids such as morphine, diamorphine, and codeine which, in all probability, act both centrally on brainstem opioid receptors and on receptors located peripherally on sensory nerve endings in the airways. However, at their effective doses they also cause physical dependence, respiratory depression, and gastrointestinal symptoms. Morphine and diamorphine are very addictive but are useful in treating severe distressing cough in patients with terminal illness such as bronchial carcinoma. Several opiate-containing proprietary cough mixtures contain low doses of weaker opioids such as codeine, but there is no strong evidence that these are more effective than the demulsant vehicle.

Non-narcotic antitussive agents

Dextromethorphan is the dextro isomer of the opiate levomethorphan and it has no analgesic or sedative properties. Dextromethorphan is the most commonly used antitussive in the USA. Orally administered dextromethorphan is as effective as codeine in suppressing cough and has been used as a constituent of many OTC preparations. Furthermore, recent reports suggest that patients with an opioid resistant cough achieved symptomatic relief with the peripherally acting non-opioid drug benzonatate. Levodropropizine, oxalamine, and prenoxdiazine are available as cough treatments in Europe. Clinical studies have shown favourable data with levodropropizine in cancer related cough.

Local anaesthetics

Local anaesthetics such as lignocaine are delivered locally to the airways and have been shown to attenuate capsaicin induced cough in humans. However, the effect is transient and the antitussive effect is accompanied by oropharyngeal anaesthesia leading to an increased risk of aspiration of airway secretions and food. This treatment should be avoided in patients with asthma because it may induce severe bronchoconstriction. Interestingly, lozenges containing local anaesthetics are often used as OTC treatment for acute cough such as that following an upper respiratory tract infection.

Menthol

Menthol has been proposed as an antitussive treatment and has been shown to inhibit citric acid induced cough in normal volunteers, but to a lesser extent than lignocaine. However, it has advantages over lignocaine as menthol does not result in oropharyngeal anaesthesia and may therefore be a more selective antitussive treatment.

NEW TREATMENTS

New drugs for the treatment of cough may be directed at an extremely heterogeneous group of targets. A major distinction in this regard is the ability of certain drugs to inhibit the underlying inflammatory process that under certain conditions cause cough—for example, anti-inflammatory drugs for the treatment of asthma or COPD or novel proton pump inhibitors as treatment for gastro-oesophageal reflux—or compounds that are targeted to inhibit sensory nerve activity directly which should, in theory, inhibit cough of any aetiology. However, here we would like to focus on compounds that can be classified as symptomatic antitussive agents which recognise as their main targets ion channels, receptors, or other molecules expressed peripherally in primary sensory neurons or by inhibition of central mechanisms.
Inhibition of prostanoid synthesis/action
The high tussive potency of the prostanoids in humans suggests that their local release in various respiratory pathophysiological conditions may be responsible for the accompanying cough/irritantcy. In patients with asthma cough thresholds with indomethacin and OKY-046 (thromboxane synthase inhibitor) treatment were significantly greater than with placebo, which supports the hypothesis that thromboxane A2 may be one of the cyclooxygenase products augmenting airway cough sensitivity in asthma. Furthermore, it has been suggested that prostanoids may have a role in the genesis of cough induced by ACE inhibitors, and inhibition of prostanoid synthesis with indomethacin or a thromboxane antagonist can reduce or abolish the incidence of this side effect. However, although prostanoids may be involved in cough associated with ACE inhibitor therapy, evidenced by the ability of the non-steroidal anti-inflammatory sulindac to inhibit cough in patients on this treatment, the same compound was ineffective in patients not on ACE inhibitor therapy but with idiopathic dry unproductive cough.

Ion channel modulators
Transient receptor potential (TRP) channels
Recently, receptors have been cloned on sensory nerves that are activated by thermal stimuli. The cold and menthol sensitive receptor (CMR1) has recently been characterised and cloned and is a member of the TRP family of excitatory ion channels. Interestingly, menthol has been proposed as an antitussive treatment and has been shown to inhibit citric acid induced cough in normal volunteers. Activators of this particular channel may therefore prove to be useful therapeutic agents. The heat sensitive channels VR1 and VR1 are TRP channels that detect temperatures over a wide range. The VR1 channel is activated by capsaicin, the main pungent ingredient in hot chilli peppers; however, the related channel VR1 does not respond to capsaicin but is activated by temperatures exceeding 50°C. Since the actions of the sensory nerve stimulant capsaicin on sensory nerves may be mediated by activation of the VR1 receptor, blocking these channels may be a good target for an antitussive treatment.

Potassium channel openers
In single fibre recording studies, NS1619, an opener of large conductance calcium activated potassium (BKCa) channels, has been shown to inhibit the firing of Aδ and C fibres innervating the guinea pig airway. In the same study the guinea pig tussive response elicited to citric acid was also inhibited by NS1619 which underlines the usefulness of this class of compounds for cough treatment in the future.

Other workers have suggested that ATP sensitive potassium channels may be a good target following studies in which openers of these channels (pinacidil and cromakalim) reduced citric acid induced cough in guinea pigs.

Chloride channels
It has been shown that frusemide can reduce the potentiation of capsaicin induced cough by prostanoid F3a (PGF2α). Frusemide had no effect on capsaicin induced cough alone. In view of these findings it has been suggested that changes in local ionic concentrations by frusemide, particularly chloride ions within the vicinity of epithelial cough receptors, may be responsible for this inhibitory effect.

CONCLUSIONS
Treatment of the underlying cause of cough can often be effective—for example, inhaled corticosteroids for asthma related cough. However, at the moment there are no effective treatments controlling the cough response per se with an acceptable therapeutic ratio. There is therefore a need for
more selective drugs with a favourable side effect profile. The future looks promising with identification of several new mechanisms which may lead to new drugs that target the increased sensitivity of sensory fibres resulting in exaggerated cough.

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