

EDITORIAL

H⁺/K⁺-ATPase (proton pump) inhibitors dampen increased cough reflex: more than gastric acid suppression

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Cough is one of the most frequent reasons for seeking a consultation with a doctor, and a cough lasting for more than 3 weeks may be related to a variety of pulmonary and non-pulmonary causes that include asthma, chronic rhinosinusitis, and gastro-oesophageal reflux (GOR) [1]. The mechanisms by which these conditions produce persistent cough are unclear, though it is likely that there is a common pathway linking these associated causes with the occurrence of an enhanced cough reflex. This points towards an increase in the general excitability of the nervous pathways of cough, a process that may occur both at the cough receptor level or centrally at the level of the central coordination of the cough reflex [2, 3]. Treating the associated cause of chronic cough sometimes, but not always, leads to significant relief of the symptom.

GOR, the movement of acid and other components of gastric contents from the oesophagus into the larynx and trachea, is one of the most commonly-associated cause of chronic cough in all age groups. GOR may lead to symptoms or physical complications such as heartburn, chest pain, a sour taste, or regurgitation, and also a chronic persistent cough. The primary causes of GOR-associated cough could be aspiration of refluxed gastric contents including acid to cause direct stimulation of laryngeal or airway cough receptors, direct stimulation of vagally innervated lower oesophageal receptors by the gastric contents to induce a distal oesophageal–tracheobronchial reflex, and possibly oesophageal dysmotility problems [4]. The oesophageal–tracheobronchial cough reflex mechanism has been proposed on the basis of studies in which distal oesophageal acid perfusion induced coughing episodes in such patients [5]. Over 90% of the cough episodes have been shown to be temporally related to reflux episodes. A high proportion of patients with GOR also appear to have gastrohypopharyngeal reflux, and there may be a direct effect of acid reflux on cough receptors in the larynx and trachea. Coughing itself may precipitate reflux, setting a vicious circle of acid inducing cough, which in turn induces acid reflux. Continuous monitoring of tracheal and oesophageal pH in patients with symptomatic GOR has demonstrated significant increases in tracheal acidity with pH's falling down to 4 during episodes of reflux [6].

Reduction in gastric acid production has been an important part of therapy of GOR, and of cough associated with GOR. In open uncontrolled studies, histamine-H₂ blockers and proton pump inhibitors have been reported to be very successful but more recent placebo-controlled double-blind trials have confirmed benefit but to a lesser extent [7, 8]. This could be as a result of the presence of other components of the refluxate such as pepsin that could activate cough.

The gastric H⁺/K⁺-ATPase is a proton pump that is responsible for gastric acid secretion and that actively transports protons and K⁺ ions in opposite directions to generate in excess of a millionfold gradient across the membrane under physiologic conditions. The mechanism of action of these proton pump inhibitors in suppressing cough is attributed to inhibition of H⁺/K⁺-ATPase in the gastric mucosa, resulting in suppression of gastric acid output. This leads to a reduction in stimulation of pharyngeal and/or laryngeal or tracheal cough receptors or alternatively to lesser activation of lower oesophageal neural terminals that may link directly to airway cough receptors.

In this issue, Oribe et al. [9] have examined whether these H⁺/K⁺-ATPase inhibitors can inhibit enhanced cough reflex. They used the conscious allergic guinea-pig which when exposed to allergen develops an enhanced cough response to capsaicin. This has turned out to be the best animal model for cough, not least because it is one of the few rodent species that actually cough to tussive stimuli such as capsaicin and citric acid; in addition, its cough pathways have been relatively well studied [10]. The increase in cough hypersensitivity to capsaicin was augmented following allergen exposure and was partly inhibited by two different H⁺/K⁺-ATPase inhibitors, omeprazole and rabeprazole, but not by an H₂-histamine receptor antagonist, cimetidine. These effects were not accompanied by any inhibition of allergic inflammation or changes in bronchoalveolar lavage H⁺ concentrations, which both increased following allergen challenge. The authors could not demonstrate any H⁺/K⁺-ATPase expression in the airway mucosa, raising the issue of site of action of the proton pump inhibitors. Presumably inhibition of gastric acid was not the most important issue since cimetidine, which also inhibits gastric acid secretion, had no effect.

These observations are intriguing, and raise several issues that should open up novel directions of research in the area of protons, cough sensitivity and the role of H⁺/K⁺-ATPase. H⁺/K⁺-ATPase is now associated with the development of cough hypersensitivity, and inhibition of H⁺/K⁺-ATPase may be more generally considered as a treatment for chronic cough. Although this work suggests that proton inhibitors may be effective for cough associated with allergic inflammation (such as in asthma, allergic cough or cough-variant asthma), it is possible that it could apply to other forms of chronic cough. In support of this, an increase in H⁺ ions has been reported in exhaled breath condensates of patients with chronic cough associated with a wide variety of causes [11]. This study is also relevant to GOR-associated cough since these patients also demonstrate an enhanced cough response [12, 13]. It would be useful to develop a GOR model in the guinea-pig.

Protons may open up various ion channels in afferent nerves, such as transient receptor potential vanilloid receptors, which are stimulated by capsaicin [14] to induce Ca^{++} influx which could result in cough. There is therefore a potential for H^+ ions in augmenting capsaicin cough sensitivity. An increase in the expression of transient receptor potential vanilloid-1 in epithelial airway nerves of chronic cough patients has been recently reported [15]. Oribe et al. [9] prefer the explanation that other ATPases in the airways presumably inhibited by proton pump inhibitors are also important in transporting protons across membranes to regulate pH, and they mention the possibility of vacuolar H^+ -ATPase which also mediate ATP-dependent transport of protons as being important [9]. Such a possibility could have been checked using specific inhibitors of vacuolar H^+ -ATPase. However, H^+/K^+ -ATPase have been previously reported in the airways. H^+/K^+ -ATPase has been localized in serous cells and ducts of submucosal glands in the larynx [16] and in airway smooth muscle cells of guinea-pig and humans, H^+/K^+ -ATPase inhibitors induce relaxation [17]. The presence of these ATPases in the airways may be important sites for the action of the proton pump inhibitors. They do not exclude the possibility that H^+/K^+ -ATPase may be present in the cough receptor. A Na^+/K^+ -ATPase has been described in cough receptor, and proposed to play an essential role in regulating the excitability of the cough receptor [18].

H^+/K^+ -ATPase proton pump inhibitors may have wider implications in the treatment of chronic cough than just specifically targeted for GOR-associated cough. Its site of action may not be limited to just inhibition of gastric acid, but may be important in H^+ homeostasis at neuronal sites involved in the cough reflex. It remains to be seen whether these inhibitors possess more generalized inhibition of the enhanced cough reflex characteristic of chronic cough. Further work is needed regarding the role of H^+/K^+ -ATPase in the induction of cough.

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