Pulmonary Pharmacology & Therapeutics 26 (2013) 486–490

Contents lists available at SciVerse ScienceDirect

Pulmonary Pharmacology & Therapeutics

journal homepage: www.elsevier.com/locate/ypupt

Regulating cough through modulation of sensory nerve function in the airways

D. Spina*, C.P. Page

The Sackler Institute of Pulmonary Pharmacology, Institute of Pharmaceutical Science, King's College London, London SE1 9NH, United Kingdom

ARTICLE INFO

Article history:
Received 2 December 2012
Received in revised form
7 March 2013
Accepted 12 March 2013

Keywords:
Cough
Opioid
Local anaesthetic
TRPV1
TRPA1
Afferent nerves

ABSTRACT

Whilst local anaesthetics when applied directly to laryngeal nerves or topically to the lung can suppress cough, their chronic use is constrained because of dose limiting side effects. However, the effectiveness of local anaesthetics suggests that selectivity targeting nerves in the airway may provide novel approaches for the treatment of cough in the future. There is a considerable wealth of evidence showing that there are different afferent nerve subtypes in the airways. Traditionally C-fibres have been the focus of much research in the cough field since the stimulation of these afferents by capsaicin is able to elicit cough in guinea-pigs and in man, and drugs targeting various proteins expressed in these nerves (e.g. mu-opioid, NOP1, TRPV1, sodium channels) have been shown to be anti-tussive in preclinical models of cough. However, interest in Aδ fibres has increased recently in light of the discovery of a specific cough receptor in the guinea-pig that is provoked by citric acid and punctate stimulation, but not capsaicin and which has been anatomically linked to Aδ fibres. There is also some evidence that as a result of inflammation in the airways, Aδ fibres can begin to express neuropeptides and TRPV1 receptors so that they can become responsive to endogenous activators of this ion channel and to irritants like capsaicin. Consequently, there is considerable interest in targeting either one or both afferent nerve types for the treatment of chronic cough. However, to date the translation of preclinical studies into man has largely been disappointing and certainly there is a need for better preclinical models in this field. There also remain many challenges to overcome at a clinical level, such as what patient group(s) should be used to assess anti-tussive drugs and whether the use of irritants that induce cough in healthy volunteers (such as citric acid or capsaicin) is of any value in the assessment of novel anti-tussive drugs. The development of several continuous monitoring methodologies for measuring cough will hopefully allow better evaluation of treatments in patients with chronic cough. Nonetheless, cough remains a major unmet clinical need in respiratory medicine where new drugs are urgently required.

1. Introduction

Whilst acute cough (lasting a few weeks) is not a serious clinical problem, it is the most common respiratory ailment for which patients seek medical help and several billions of dollars are spent per annum in the USA on cough remedies, many of which remain either unproven or are dosed too low to be clinically effective. In contrast, chronic cough (persisting more than 8 weeks) can be a debilitating condition estimated to affect some 9–33% of the population and can be a symptom of a variety of pulmonary conditions producing an adverse effect on quality of life. Treatment of the underlying disease often resolves chronic cough, but this can take several months, during which time effective anti-tussive treatment would be desirable. Furthermore, there remains a significant cohort of patients for which there is no identifiable cause or if known, it is thought to be a consequence of cough hypersensitivity via unknown mechanisms [1]. In these individuals, there are no really effective treatment options and current anti-tussive drugs are not satisfactory.

Current treatment involves the use of opiates and dextromethorphan. However, their clinical effectiveness is still debated and more importantly hampered by dose-limiting side effects such as sedation, constipation and following long term use, addiction. The discovery of novel anti-tussive agents has been hindered by a lack of widespread interest in the pharmaceutical field to invest in drug development programmes, despite the large amounts of money spent by patients on over the counter medications for the

Abbreviations: ASIC, acid sensing ion channel; COPD, chronic obstructive pulmonary disease; NOP1, nociceptin/orphanin opioid like receptor 1; RAR, rapidly adapting receptor; RSD931, carcanium chloride; SCH 486757, 8-[bis(2-chlorophenyl)methyl]-3-(2-pyrimidinyl)-8-azabicyclo[3.2.1.]octan-3-ol; TRPV1, transient receptor potential vanilloid 1; TRPA1, transient receptor potential ankyrin 1.

* Corresponding author. Tel.: +44 2078484341; fax: +44 2078484500.
E-mail address: domenico.spina@kcl.ac.uk (D. Spina).

1094-5539/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.pupt.2013.03.011

treatment of this symptom. This situation is also not helped by the many disappointing clinical trial results of novel anti-tussive agents which has highlighted our continuing lack of understanding of the mechanisms which are responsible for chronic cough. This lack of translation between preclinical models and relevant disease cohorts, and uncertainty concerning which disease cohort to evaluate potential novel anti-tussive agents (Table 1) has hindered drug development programmes.

2. Airway sensory nerves and cough

The afferent innervation of the mammalian lung is relatively well understood and has been described in detail elsewhere [2,3]. Briefly, the airway epithelium and mucosa is innervated by different subpopulations of afferent fibres, broadly sub-divided into Aδ and C-fibres. Within the Aδ fibre population two different nerve types have been found including slow conducting Aδ fibres and rapidly adapting receptors (RAR's), which innervate the larynx, trachea and extrapulmonary airway, with RAR's also innervating intrapulmonary airways. Aδ fibres respond to a variety of stimuli including acid, punctate stimuli and electrical stimulation to evoke cough, whilst the slowly conducting Aδ fibres do not respond to contraction of airway smooth muscle. Both subpopulations of Aδ fibres project to the nodose ganglion. Similarly, there are two subpopulations of C-fibres (implicated in the sensitisation of cough, directly involved in cough and reflex bronchoconstriction induced by bradykinin, adenosine and capsaicin). C-fibres innervating the trachea and extrapulmonary bronchi project to the jugular ganglion, whilst intrapulmonary C-fibres project to both jugular and nodose ganglion. Their direct role in cough is disputed, and it has been suggested that cough caused by capsaicin is due to secondary activation of RAR's following odema and/or bronchoconstriction [2]. Interestingly, sensory neuropeptides do not appear to directly activate the slowly conducting Aδ fibre population in the extrapulmonary airways [3] and studies in dogs have shown that activation of pulmonary C-fibres can suppress cough induced by mechanical irritation of the tracheal mucosa in the cat [4,5]. In contrast, activation of C-fibres in the intrapulmonary airways in guinea-pigs can augment cough reflex responses, presumably by acting synergistically with Aδ fibre stimulation at the level of the brain stem [3].

It is clear that sensory nerve hypersensitivity accounts for the increased cough frequency observed in subjects with asthma, COPD, post-viral cough or much of interstitial lung disease [6]. The mechanism of this hypersensitivity is not completely understood, but it has been shown that there is an increase in expression of TRPV1 on airway sensory nerves in patients with idiopathic cough [7], and the concentration of neurotrophin derived and brain derived neurotrophic factors were elevated in sputum of individuals with idiopathic pulmonary fibrosis [8]. How these and other changes in sensory nerve biology lead to hypertussive cough is not well established in man, but a number of observations in preclinical studies have suggested potential mechanisms that may operate in human disease. During inflammation, numerous substances are released that have been shown to activate TRPV1 (e.g. certain lipid mediators), B2 receptors (bradykinin), TRPA1 (e.g. certain prostaglandins and some chemicals in cigarette smoke such as acrolein) and ASIC's (e.g. low pH during inflammation) could give rise to an increase in C-fibre traffic to the brain stem, resulting in a gain in function (analogous to the wind-up mechanisms described in chronic pain) and the expression of cough hypersensitivity. Alternatively, the inducible expression of proteins (e.g. TRPV1) in Aδ fibres might directly link the inflamed airway with the heightened cough response. For example, animal studies have shown that following allergen challenge, Aδ fibres express TRPV1 highlighting the plastic nature of afferent nerves within the lung and the potential of stimulating the 'cough' receptor directly by endogenously

Table 1
Examples of the preclinical and clinical effectiveness of novel anti-tussive agents.

Drug	Target	Preclinical studies		Clinical studies: healthy subjects		Clinical studies: chronic cough
		Stimulus	Outcome	Stimulus	Outcome	Outcome
Lidocaine	Na_v channels, TRPV1, TRPA1	Capsaicin[1]; Citric acid[1]	No effect (3% solution) [17]; 50% inhibition (1% solution) [17]	Capsaicin; Citric acid	60% Inhibition (4% solution) [12]; 60% Inhibition (4% solution [12]	COPD (60% reduction in the cough severity score; 0.25%/kg) [55]
RSD931	NE	Capsaicin[1]; Citric acid[1]; Citric acid[2]	75% inhibition (3% solution) [17]; 100% inhibition (1% solution) [17] 85% inhibition (1% solution) [17]		Not known	Not known
Opiates	μ-opioid	Citric acid[1]	80% inhibition (64 mg/kg) [20]	Capsaicin	2 fold shift in CR2. No effect on CR5 (codeine; 60 mg; 0.15 mg/kg morphine) [18]	40% decrease in CQLQ scores. No effect on CR2 or CR5 for citric acid (morphine sulphate, 5 mg, tid) [21]
Gabapentin	Ca_v (α2δ) channels	NE		NE		20% decrease in cough number. No effect on CR5 for capsaicin (1800 mg daily) [51]
Thalidomide	NE	NE		NE		20% decrease in CQLQ score (50 or 100 mg daily) [52]
Nociceptin	NOP1	Citric acid[1]; Mechanical stimulation[3]	80% inhibition (3 mg/kg) [28]; 60% inhibition (1 mg/kg) [30]	NE		NE
SCH 486757	NOP1	Capsaicin[1]; Mechanical stimulation[3]	70% inhibition (1 mg/kg) [56]; 60% inhibition (300 μg/kg) [56]	NE		Non significant reduction in cough number in post-viral cough (100 mg tid daily) [32]

CR: cough reflex sensitivity. CR2 and CR5 refer to the concentration of tussive agent required to induce 2 or 5 coughs respectively.
CQLQ: cough quality of life questionnaire.
Species used in preclinical studies include, guinea-pig[1], rabbit[2] and cat[3].
NE: not evaluated.