



The effect of pain conditioning on experimentally evoked cough: evidence of impaired endogenous inhibitory control mechanisms in refractory chronic cough

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Painful cold-water hand immersion elicited a weaker inhibitory effect on cough in patients with refractory chronic cough than healthy volunteers, suggesting a relative deficiency in conditioned pain modulation <https://bit.ly/3gedtjg>

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ABSTRACT The pathophysiology of refractory chronic cough (RCC) is unclear. We hypothesised that endogenous inhibitory control mechanisms, such as those activated by noxious stimuli inducing pain (conditioned pain modulation) may be capable of inhibiting coughing and urge to cough evoked by inhaled capsaicin. Furthermore, these mechanisms may be impaired in patients with RCC.

The objective was to investigate the effects of pain on cough and urge to cough in healthy volunteers and RCC patients. Healthy volunteers and RCC patients underwent a randomised, controlled, four-way crossover study comparing the effect of four interventions on capsaicin-evoked coughing and urge to cough. The interventions comprised immersing a hand in 1) noxious cold water; 2) warm water; 3) warm water, but subjects were instructed to voluntarily suppress coughing; and 4) no intervention. The co-primary outcomes were numbers of evoked coughs and urge to cough scores.

20 healthy volunteers (mean±SD age 50.1±14.2 years, male:female 10:10) and 20 RCC patients (age 60.1±7.9 years, male:female 9:11) participated. Overall, noxious cold water reduced capsaicin-evoked urge-to-cough scores and cough numbers compared with warm water (1.6 (95% CI 1.3–2.0) *versus* 2.2 (1.8–2.6), $p<0.001$ and 4.8 (3.7–6.2) coughs *versus* 7.9 (6.7–9.5) coughs, $p<0.001$, respectively). Healthy volunteers and RCC patients demonstrated similar reductions in the urge to cough during noxious cold-water immersion, but noxious cold water and voluntary suppression interventions were less effective at reducing capsaicin-evoked cough in RCC patients than in healthy volunteers ($p=0.041$).

Endogenous inhibitory control mechanisms, specifically those activated by pain, can reduce both coughing and the urge to cough. Impairment of endogenous inhibitory control mechanisms may contribute to excessive coughing in RCC.

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Introduction

Chronic cough is one of the most common reasons for referral to a pulmonologist and has a global prevalence of ~10% [1]. Unfortunately, there are no licenced treatments for this debilitating condition and the underlying mechanisms are poorly understood. Cough is a reflex designed to protect the airway from mechanical and noxious chemical irritants, but is also under a degree of voluntary control. Patients with chronic cough complain that their cough is driven by sensations of irritation in the throat and an urge to cough.

A number of mechanistic and clinical translational studies have reported evidence of neuronal hyperexcitability to inhaled irritant stimuli in refractory chronic cough (RCC) [2, 3]. We have shown that RCC patients predominantly exhibit a hyperresponsiveness (rather than hypersensitivity) of cough responses to inhaled capsaicin [3], *i.e.* they cough approximately twice as frequently in response to a range of doses of inhaled capsaicin compared with healthy controls. These heightened cough responses observed in chronic cough have been compared to the hyperalgesia exhibited by patients with chronic neuropathic pain.

In the study of neuropathic pain, it is thought that heightened neuronal responses occur as a consequence not only of hyperexcitability of afferent sensory pathways, but also due to failure of endogenous pain control mechanisms [4]. These mechanisms involve descending pathways that project from specific brain areas to the spinal cord where they may either facilitate or inhibit transmission of noxious information, thus determining the level of pain experienced. Interestingly, spinal neurones have been shown to be inhibited by nociceptive stimuli applied outside their own receptive fields, a phenomenon previously known as diffuse noxious inhibitory controls, and more recently termed conditioned pain modulation (CPM) [5]. For example, it can be demonstrated experimentally that a localised tonic noxious stimulus applied to the left hand will, *via* CPM, inhibit the level of pain experienced when a second noxious stimulus is applied to the right hand [6, 7]. The inhibition of pain in the right hand represents a diffuse analgesic effect (all viscera) that persists beyond the stimulation period and is independent of the site of the initial noxious stimulus.

Impaired CPM mechanisms have been found in a number of conditions including irritable bowel syndrome [8], fibromyalgia [9], chronic tension headaches/migraine [10, 11] and temporomandibular joint dysfunction as well as chronic neuropathic pain [12]. The study of CPM mechanisms has been useful in quantifying an individual's endogenous inhibition of pain, and has provided insights into disease mechanisms and treatment effects [13]. However, the effectiveness of CPM-like mechanisms in modulating airway sensations and reflexes, *e.g.* "pain inhibiting cough" has not been investigated either in healthy volunteers or in patients with RCC. Therefore, the objectives of this study were to assess whether similar inhibitory mechanisms are applicable to experimentally evoked urge to cough and coughing and whether a deficiency in these mechanisms occurs in patients with RCC compared with healthy volunteers.

Methods

Subjects

Patients with RCC were recruited from a tertiary referral specialist cough clinic (Manchester, UK) and were defined by having a cough lasting >8 weeks that was either unexplained or refractory to treatment of identified underlying conditions as per British Thoracic Society/European Respiratory Society/American College of Chest Physicians guidelines [14–16]. We excluded current smokers or ex-smokers with a >10 pack-year history, those with a recent upper respiratory tract infection (<4 weeks), pregnancy, breastfeeding, diabetes and use of medication which may have altered cough responses (*e.g.* angiotensin-converting enzyme inhibitors, opiates, gabapentin, anticholinergics and theophylline). Healthy subjects were recruited by poster advertisements and from volunteer databases. They had normal lung function and no current or past history of respiratory disease, chronic pain, irritable bowel syndrome, chronic headaches, reflux disease, post-nasal drip or psychiatric illness. The protocol was approved by the local research ethics committees (REC10/H1003/104) and registered at www.controlled-trials.com (ISRCTN31901405). All participants provided written informed consent.

Study protocol and procedures

All participants attended for two initial screening visits, followed by four randomised visits separated by ≥48 h (figure 1). At screening, after performing history and examination, all participants completed several questionnaires (full list is available in the supplementary material). The irritable bowel syndrome

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This study is registered at www.isrctn.com with clinical trial identifier ISRCTN31901405.

(IBS) subsection of the Rome III questionnaire was completed by all participants, and healthy volunteers were excluded if they met the criteria for IBS, because CPM mechanisms are known to be impaired in IBS patients [8, 17]. Participants were then fitted with an ambulatory cough monitor (VitaloJAK; Vitalograph, Buckingham, UK) for the next 24 h, and returned ≥ 1 day later to undergo a full-dose capsaicin cough challenge as described previously [3, 18]. The dose of capsaicin that evoked at least half the maximum cough response (ED_{50}) during the full challenge was chosen as the single dose to be administered in the four subsequent visits. Prior to the randomised visits, all subjects practised placing their nondominant hand in a water bath (NE4 Clifton stirred water bath; Nickel-Electro Ltd, Weston-super-Mare, UK) in which the temperature was set to 10°C (accurate to $\pm 0.5^\circ\text{C}$) for 1 min 30 s if possible, but the hand could be withdrawn if the pain became unbearable at any stage. This cold-water immersion method is known as heterotopic noxious counter-stimulation and has been used extensively to activate CPM mechanisms when studying pain [19, 20]. In addition, subjects practised rating pain intensity using a numerical scale ranging from 0 (no pain) to 10 (worst possible pain).

All subjects then attended four randomised visits in a crossover design, wearing the ambulatory cough monitor throughout (figure 1). At each visit, subjects underwent two cough challenges 1 h apart; each challenge was performed while the subject had their hand immersed in either noxious cold water (10°C), non-noxious warm water (32°C) or no immersion (no intervention). The order of the cold water and voluntary cough suppression intervention blocks were randomised. Subjects were instructed to place their hand in the water bath (or not for no intervention) and then after 20 s inhale the predetermined ED_{50} dose of capsaicin four times at 15-s intervals, while the hand remained immersed. During the cold-water immersion and no-intervention blocks, subjects were instructed to cough freely; however, during one of the warm water immersions subjects were told to “try not to cough”. The number of coughs evoked was counted, and the intensity of the urge to cough experienced was rated on a modified Borg scale (0–10) (figure 1) [21, 22]. Pain intensity was rated on a numerical scale (0–10) immediately prior to the first inhalation and after the last inhalation of capsaicin. This procedure was then repeated an hour later to

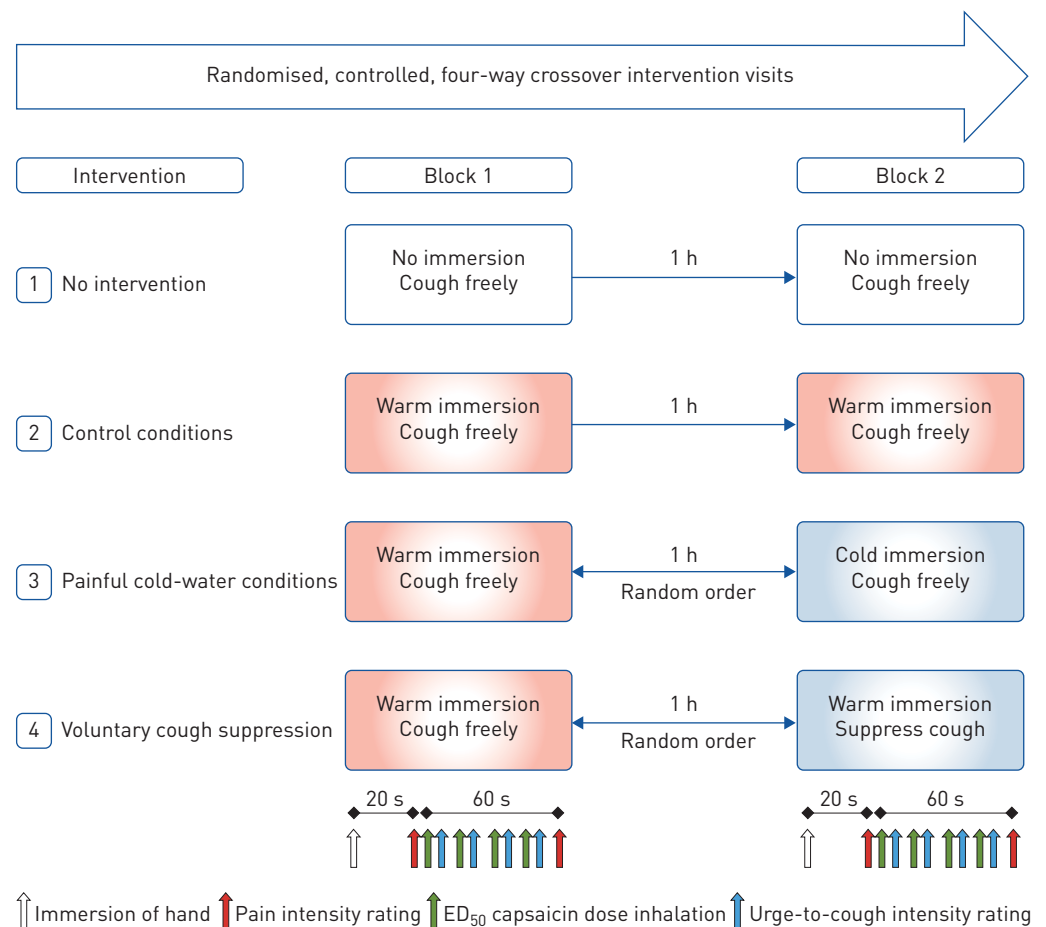


FIGURE 1 Study design. ED_{50} : dose evoking at least half the maximum evoked coughs.

ensure the stability of ED₅₀-evoked coughs. Blood pressure and pulse rate were measured before and after each intervention block. The number of coughs evoked was later verified from the sound recordings.

Statistical analysis

Data analysis was performed using SPSS version 25.0 (IBM, Armonk, NY, USA). Summary data are presented as mean±SD or as median (interquartile range). Repeatability of both cough and urge to cough evoked by the ED₅₀ capsaicin concentration was assessed using intraclass correlation estimates, calculated using data collected from the warm water hand immersion where blocks 1 and 2 were identical and separated by 60 min (average measures $k=2$, absolute agreement, two-way mixed-effects model). The effect of the interventions (warm water, noxious cold water, no intervention), instructions (cough *versus* try not to cough), disease group on both urge to cough and capsaicin-evoked coughs were analysed using general estimating equations (GEE, linear and nonlinear) with a Bonferroni correction for multiplicity of *post hoc* comparisons.

Results

Subjects

20 healthy controls and 20 RCC patients completed the study between January and October 2011. There was no significant difference in age, forced expiratory volume in 1 s % predicted, forced vital capacity % pred, pack-years of previous smoking history or body mass index between the groups (table 1). However, RCC patients demonstrated significantly higher scores on the sino-nasal outcome test [23] and gastro-oesophageal reflux disease questionnaires compared to healthy volunteers [24].

As expected, patients with RCC demonstrated exaggerated and hypersensitive cough responses indicated by a significantly higher maximum number of evoked coughs, and lower ED₅₀ by one double dose (table 1). This was associated with a higher 24-h cough frequency in RCC patients, with the greatest difference during waking hours. In addition, patients with RCC had significantly higher anxiety and depression scores compared to healthy volunteers, but no significant group differences for perceived stress, body vigilance or pain catastrophising (supplementary table E1).

Repeatability of end-points

There were no missing data for either cough frequency or the urge to cough. The urge-to-cough scores and cough frequency measures exhibited very good repeatability. The mean±SD difference in the urge-to-cough sensation with capsaicin inhalations 1 h apart during the warm-water hand immersion was 0.10±1.07 on the modified Borg scale, with an intraclass correlation coefficient of 0.88 ($p<0.001$). The

TABLE 1 Subject demographics and baseline characteristics

| | Healthy volunteers | RCC | p-value |
|--|--------------------|------------------|---------|
| Subjects | 20 | 20 | |
| Age years | 50.1±14.2 | 60.1±13.2 | 0.22 |
| Male:female | 10:10 | 9:11 | |
| Duration of cough years | | 13.0±9.8 | |
| BMI kg·m⁻² | 26.6 | 28.1 | 0.25 |
| Smoking pack-years | 0.0 (0.0–0.0) | 0.0 (0.0–1.8) | 0.44 |
| FEV₁ % pred | 105.7±13.8 | 98.8±16.5 | 0.16 |
| FVC % pred | 107.8±16.0 | 102.7±15.5 | 0.31 |
| SNOT score | 0.08±0.5 | 1.3±1.4 | <0.001 |
| GORD score | 0.0±3.5 | 7.0±15.5 | <0.001 |
| CQLQ | | 52.5±12.8 | |
| Capsaicin E_{max} | 14.0 (10.5–18.8) | 27.5 (21.3–37.0) | <0.001 |
| Capsaicin ED₅₀ μM·L⁻¹ | 15.6 (7.8–31.3) | 7.8 (3.9–15.6) | <0.001 |
| 24-h cough frequency coughs·h⁻¹ | 0.8 (0.2–1.3) | 10.9 (8.3–23.7) | <0.001 |
| Awake cough frequency coughs·h⁻¹ | 1.1 (0.3–1.8) | 15.4 (12.2–26.7) | <0.001 |
| Sleep cough frequency coughs·h⁻¹ | 0.1 (0.0–0.6) | 1.8 (0.5–5.5) | <0.001 |

Data are presented as n, mean±SD or median (interquartile range), unless otherwise stated. RCC: refractory chronic cough; BMI: body mass index; FEV₁: forced expiratory volume in 1 s; FVC: forced vital capacity; SNOT: sino-nasal outcome test; GORD: gastro-oesophageal reflux disease; CQLQ: cough quality-of-life questionnaire; E_{max}: maximum evoked coughs at any dose of capsaicin; ED₅₀: dose evoking at least half the E_{max}.

mean \pm SD difference in the number of capsaicin-evoked coughs over four inhalations 1 h apart in the same conditions was 2.5 \pm 7.6 with an intraclass correlation coefficient of 0.79 ($p<0.001$).

Factors influencing evoked cough and urge to cough

The factors influencing the co-primary end-points were explored in the whole dataset (healthy controls and RCC patients), using GEE modelling (urge-to-cough linear model, coughs Poisson model). Overall, the urge-to-cough ratings during inhalation of capsaicin ED₅₀ doses were not influenced by age ($p=0.71$) or sex ($p=0.87$). In contrast, the numbers of coughs evoked by the ED₅₀ capsaicin concentration increased slightly with increasing age ($B=0.021$, $p=0.006$), but were not influenced by sex (females 6.6 (4.9–9.0) coughs *versus* males 7.3 (5.5–9.3) coughs; $p=0.61$). Additionally, the urge to cough ($B=0.26$, $p<0.001$) significantly predicted the number of coughs evoked.

Effect of noxious cold stimulus and voluntary suppression on evoked urge to cough

A GEE model (linear) showed a significant effect of the interventions on the urge to cough ($p<0.001$) in the combined subject groups (figure 2a). Noxious cold-water immersion significantly reduced the urge to cough compared with warm-water immersion (1.6, 95% CI 1.3–2.0 *versus* 2.2, 95% CI 1.8–2.6; $p<0.001$), cough suppression during warm-water immersion (2.2, 95% CI 1.7–2.7; $p=0.02$) and no intervention (2.4, 95% CI 1.8–3.0; $p=0.002$) (figure 2a). There were no significant differences between the urge to cough with warm-water immersion, cough suppression during warm-water immersion and no intervention. There were no significant effects of intervention sequence or period.

Effect of noxious cold stimulus and voluntary suppression on evoked cough

A GEE model (Poisson) showed a significant effect of the interventions on number of coughs evoked by inhaling the ED₅₀ dose of capsaicin ($p<0.001$), adjusted for the influences of age ($p=0.005$) and urge to cough ($p<0.001$). In the combined data (all subjects), noxious cold-water immersion significantly reduced the number of evoked coughs compared with warm-water immersion control (4.8, 95% CI 3.7–6.2 coughs *versus* 7.9, 95% CI 6.7–9.5 coughs; $p<0.001$). Voluntary cough suppression had a similar inhibitory effect on coughing (3.8, 95% CI 2.3–6.3 coughs; $p<0.001$), whereas no intervention was similar to warm-water immersion (6.7, 95% CI 5.3–8.4 coughs; $p=0.06$) (figure 2b). There were no significant effects of intervention sequence or period in the model.

Comparison of RCC patients with healthy volunteers

Interestingly, there were no significant differences in urge to cough reported by RCC patients compared with healthy volunteers when inhaling the ED₅₀ capsaicin concentration. Both groups experienced a similar reduction in urge to cough during cold-water immersion compared with the warm water, cough suppression with warm water and no intervention (figure 3a) ($p<0.001$). In contrast, despite reporting similar urge to cough, RCC patients coughed much more frequently than healthy volunteers during all the interventions (figure 3b) (healthy volunteers 3.4 (2.3–4.9) coughs *versus* RCC 9.1 (7.5–11.1) coughs; $p<0.001$). The effect of the interventions also differed between the patient groups (group*intervention interaction; $p=0.042$). *Post hoc* comparisons corrected for multiplicity (Bonferroni) suggested that while the different interventions significantly modulated the number of evoked coughs in the healthy volunteers group, *i.e.* cold-water immersion and voluntary suppression both significantly reduced coughing compared with warm-water immersion and no intervention, this was not the case for RCC. In the RCC group,

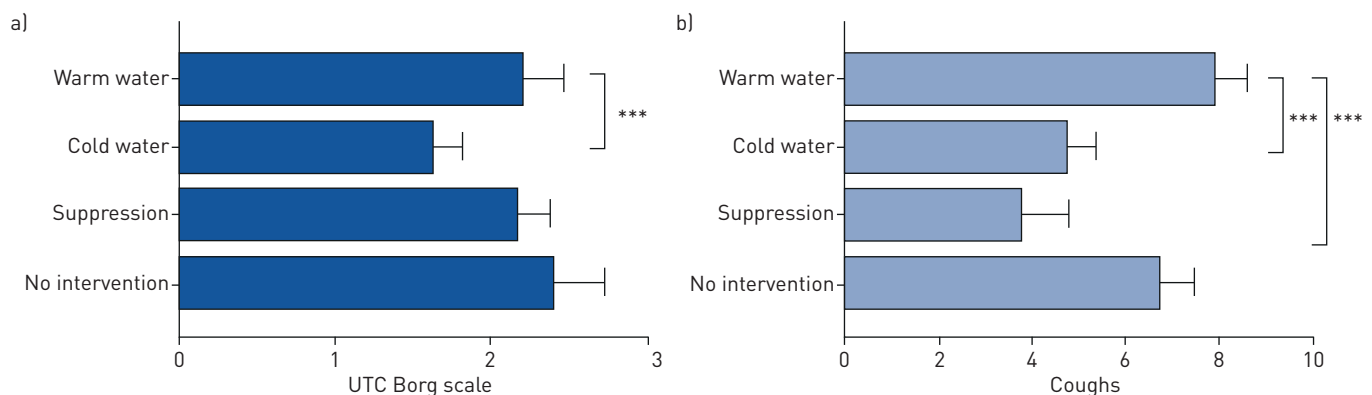


FIGURE 2 Overall effects of all interventions on a) urge to cough (UTC) and b) capsaicin-evoked cough in all participants ($n=40$). Data are presented as mean \pm SEM. ***: $p<0.001$ in comparison with warm-water control.

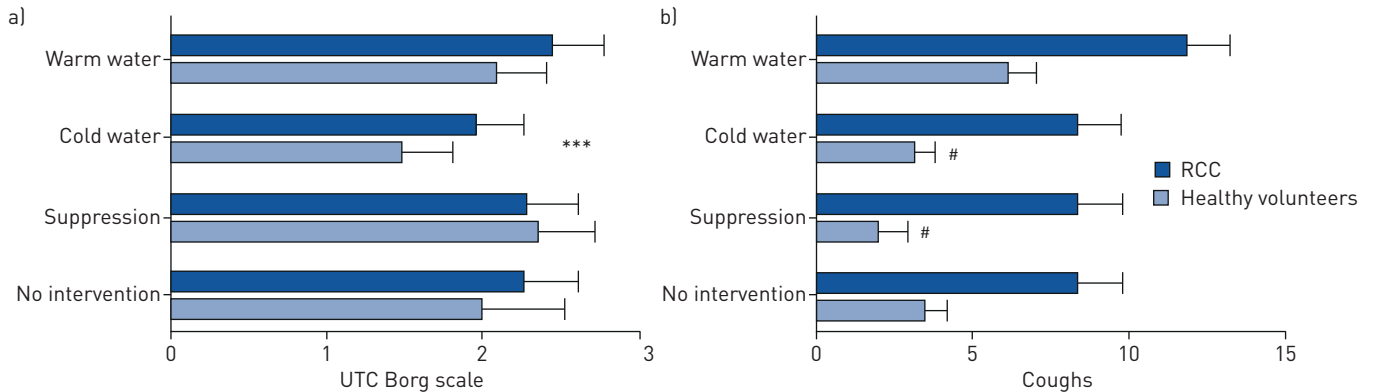


FIGURE 3 The effects of all conditions on capsaicin-evoked urge to cough (UTC) and coughing in healthy volunteers and refractory chronic cough (RCC) patients. a) For UTC, there was no difference between healthy volunteers and RCC patients; both groups experienced a similar reduction in UTC with cold-water immersion compared with warm-water immersion and other conditions. b) Evoked coughs were significantly greater in RCC patients than healthy volunteers for all conditions ($p < 0.001$), but reductions in coughing were significant for cold-water immersion and voluntary suppression in healthy controls (compared with warm water), but not in RCC patients. Data are presented as mean \pm SEM. ***: $p < 0.001$; #: $p < 0.001$.

although evoked cough was numerically reduced by these interventions, the differences did not achieve statistical significance.

Pain intensity during interventions

Pain scores were higher in RCC patients compared with healthy volunteers after the hand was immersed in noxious cold water for 20 s before any capsaicin was inhaled (3.7 ± 2.6 in healthy volunteers *versus* 5.9 ± 2.5 in RCC patients; $p < 0.001$). Pain intensity increased after the cold-water bath, but there were no differences in the change reported between the groups; mean \pm SD difference in healthy volunteers was 2.2 ± 1.7 *versus* 2.0 ± 1.5 in RCC; $p = 0.27$). During warm-water control interventions none of the subjects reported any pain.

Changes in physiology during interventions

There were no significant differences in the changes in systolic blood pressure or pulse rate between the two interventions on each study day (mean $< \pm 3$ mmHg or $< \pm 3$ bpm). There was no significance difference in the change in systolic blood pressure or pulse rate for RCC patients compared to healthy volunteers during any of the interventions (supplementary table E2).

Discussion

To our knowledge, this is the first study to directly investigate the modulatory effects of pain on coughing. Our main findings were 1) a noxious cold-water stimulus applied to the hand inhibited urge to cough and coughing induced by capsaicin inhalation; 2) asking patients to “try not to cough” also reduced capsaicin-evoked coughing, but not the urge to cough; and 3) noxious cold-water stimulus and voluntary cough suppression both appear less effective in inhibiting cough in patients with RCC compared with healthy volunteers. These findings are consistent with our hypothesis that both urge to cough and cough can be inhibited by activating endogenous inhibitory control mechanisms, unlike voluntary cough suppression, which has no influence on the urge to cough. Notably, these distinct mechanisms were both impaired in patients with RCC compared with healthy volunteers, implying failure of cough control mechanisms is more extensive than previously appreciated, and includes endogenous inhibitory controls.

Classical CPM pathways have been well characterised in both preclinical models and in translational studies in healthy volunteers and patients with well-defined neurological deficits [25, 26]. Descending inhibitory signals are thought to originate in the hypothalamus and amygdala and are transmitted *via* the periaqueductal grey (PAG) and rostroventral medulla (RVM) to the dorsal horn of the spinal cord [27–32]. The consequence of activation of these descending controls is diffuse analgesia that can be demonstrated by a reduction in the pain experienced by a second stimulus at a different site (test stimulus). Our findings provide the first evidence for an analogous endogenous inhibitory pathway activated by a remote noxious cold-water stimulus and capable of inhibiting urge to cough and coughing evoked by an inhaled irritant. While further exploration is needed to understand the exact location of the action of pain conditioning and descending inhibitory controls on cough pathways, possibilities include

the PAG, RVM and the sites where sensory airway nerves first synapse in the brainstem, *i.e.* in the nucleus tractus solitarius and paratrigenial nuclei.

Previous studies have investigated other types of cough inhibition, such as voluntary cough suppression. Healthy controls can significantly inhibit cough responses to inhaled irritants and, in comparison, RCC patients have a reduced ability to voluntarily suppress cough [33]; this finding has been replicated recently [34]. As illustrated by the current study, voluntary suppression is very different from endogenous inhibitory controls. The former is a conscious process, cognitively driven, in which patients actively try to resist coughing in response to urge to cough. The latter is subconscious, and in contrast to voluntary suppression, reduces both urge to cough and coughing in response to capsaicin.

The inability to voluntarily suppress cough is undoubtedly a problem for chronic cough patients, who often complain of a constant urge to cough. However, impaired voluntary cough suppression may well reflect the severe, persistent urge to cough experienced by chronic cough patients and thus represents an epiphenomenon rather than a fundamental component of the condition. In health, voluntary cough suppression is only important on occasions where exposure to environmental irritants occurs. Conversely, endogenous inhibitory control mechanisms (including CPM) may be tonically active, modulating perceived airway sensations and preventing inappropriate triggering of coughing episodes. Impairment of such inhibitory controls could therefore both explain the persistent urge to cough and consequential excessive coughing in RCC and is accordingly plausible as component of the pathophysiology of RCC. Of note, in this study we were only able to demonstrate a significant difference between RCC and healthy volunteers in efficiency of pain conditioning to reduce coughing. The absolute reductions in urge to cough were numerically greater in healthy controls than refractory cough patients; however, the difference did not reach statistical significance. Urge-to-cough scores are subjective and inherently more variable than cough numbers, and therefore a larger sample size would be required to demonstrate significant differences between these groups for that end-point. Of interest, RCC patients did report significantly higher pain scores on exposure to noxious cold at baseline and throughout the study compared with healthy volunteers, an observation consistent with disordered pain conditioning in this group. Whether pre-existing impaired inhibitory controls predispose individuals to developing chronic cough or occur as a consequence of the condition would be difficult to establish. Interestingly, longitudinal studies of post-operative pain support the notion that pre-existing impaired CPM predisposes subjects to develop chronic pain [35, 36]. Furthermore, studies in chronic pain states have implicated opioids in activating descending pathways mediating CPM [37], a potential explanation for the significant benefits of low-dose morphine in a substantial subset of patients with RCC.

Inhibition of cough, in the form of placebo responses, has also been observed in RCC patients participating in clinical trials of novel therapies, influencing not only subjective reports of cough severity and quality of life, but also reducing objectively measured cough frequency by ~30% [38, 39]. Like voluntary cough suppression, placebo responses are a consequence of cognitive processes, whereby the knowledge that the patient may be taking a new therapy and the expectation that this therapy may be beneficial act to reduce cough frequency. In healthy volunteers, placebo effects following placebo conditioning have been shown to reduce capsaicin-evoked urge to cough by up to 45% and a follow-up functional magnetic resonance imaging (fMRI) study suggested this was associated with increased activation in the prefrontal and posterior parietal cortices [40]. Unfortunately, fMRI studies designed to evaluate central inhibition of cough (by any mechanism) in RCC patients are lacking. A single study did compare cerebral activations during capsaicin-evoked urge to cough in RCC with healthy controls, and although voluntary cough suppression was not specifically studied, RCC patients seemed to have reduced activations compared with healthy controls in areas thought to be involved in voluntary cough suppression in healthy controls [41].

There are some limitations to this study worth noting. Firstly, a noxious cold stimulus could be considered a distraction, an alternative mechanism *via* which the urge to cough and cough could be reduced. However, this question has been addressed in classical CPM studies and distraction found to be a distinct effect from CPM [42]. Secondly, the study could not be fully blinded. By the very nature of the interventions the subjects become immediately aware of the temperature of the water bath on immersion of their hands; however, it is highly unlikely that they have particular expectations of how these may influence their cough. Finally, this first study was small in size and so has limited power to understand the effects of sex and other characteristics on the ability of noxious stimuli to modify coughing or the variability of its impairment in RCC. Nonetheless, these positive findings provide the motivation for further larger studies to characterise these endogenous inhibitory mechanisms in both health and disease and to investigate whether these changes in experimentally evoked cough also have importance in clinical spontaneous cough.

Conclusions

In conclusion, this study provides the first evidence that conditioning with a noxious stimulus modulates airway sensations and reflex responses such as the urge to cough and the cough response evoked by inhaled capsaicin. The inefficiency of this mechanism in RCC patients compared with healthy controls implicates impairment of endogenous inhibitory control mechanisms in the pathophysiology of RCC, which may be an important therapeutic target.

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