



# Chronic cough: ATP, afferent pathways and hypersensitivity

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**New evidence from tussive challenges and the P2X inhibitor gefapixant strengthens ATP as a driver of chronic cough. Cough responses to other irritants probably involve a separate peripheral activation pathway. Hypersensitivity may be due to distinct processes again.** <http://bit.ly/2YR6MuZ>

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Cough remains a vexing clinical problem in many contexts. Despite the identification of precipitating factors and relevant associated diagnoses, it is common for patients presenting to healthcare providers with persistent cough to remain unsatisfactorily treated [1]. Chronic cough is common and is associated with substantial physical and psychological morbidity [2].

A new paradigm has been suggested in recent years as a way of thinking about chronic cough, that of the cough hypersensitivity syndrome [3]. Due to largely unspecified mechanisms, peripheral and central neural pathways integral to the cough reflex are thought to be upregulated to a degree that cause otherwise innocuous stimuli to trigger coughing [4]. Precipitating factors, such as lower airway inflammation in asthma, upper airway irritation in chronic rhinosinusitis, smoking, or gastro-oesophageal reflux can clearly make coughing worse, but the primary problem is that of underlying cough hypersensitivity itself. This paradigm might explain why only a proportion of individuals with these secondary factors complain of chronic cough, and why in many cases persistent cough seems to have no driving secondary cause at all [5].

However, although very well-supported by clinical observations, cough hypersensitivity syndrome is largely a theoretical concept. The underlying mechanisms are a lot less clear, and it is one of the key areas of current cough research. Potential anatomical sites driving cough hypersensitivity include peripheral afferent nerve terminals of the airway, the jugular and nodose ganglia of the vagus nerve, the sensory integration sites in the brainstem, and higher brain pathways, each with maladaptive over-excitatory or under-inhibitory influences on the cough reflex [6]. Evidence for the role of central neural pathways is perhaps the strongest at present, and includes data from functional magnetic resonance imaging. Compared to healthy volunteers, patients with long-standing refractory cough display increased activity in specific areas of the midbrain, and underactivity in particular forebrain locations when coughing in response to inhaled capsaicin [7]. Recent observations also suggest lack of voluntary or semi-voluntary suppressive control as an important factor in refractory chronic cough [8, 9]. Furthermore, the majority of the treatments for this condition with proven efficacy to date most likely have a central site of action, including behavioural training delivered by specialist physio- and speech and language therapists [10], the antiepileptic medications gabapentin [11] and pregabalin [12], the antidepressant amitriptyline [13], and

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morphine [14]. The importance of central influences on cough is clear from the significant reduction in cough frequency in health and disease during sleep [15].

Evidence for a role of more peripheral sites in the mechanisms of cough hypersensitivity has so far been much more limited. Although a number of afferent airway receptors have been shown to play a role in the cough reflex, their contribution to the pathophysiology of chronic refractory cough has remained unclear. For example, one such receptor, TRPV1, possibly increased in expression in the airways of patients with the disease [16], now appears less important than was previously thought. Despite the observation that specific TRPV1 antagonist can successfully abolish the cough reflex induced by inhaled capsaicin, the lack of any change in daily cough frequency in patients with chronic cough tested with the same agent goes against any significant contribution of TRPV1 to the mechanism of cough hypersensitivity syndrome [17]. Very similar observations have involved the receptor TRPA1 [18].

However, knowledge of neural pathways in cough has recently been advanced through focus on another receptor, P2X3. P2X is a large family of evolutionarily conserved ATP-gated ion channels present in a range of organisms and tissue types [19]; P2X3 is a subtype present in the airways on the terminals of sensory nerves [20]. In 2005, work in guinea pigs demonstrated the provocation of cough by the inhalation of ATP, and the attenuation of this response by the administration of P2X inhibitor [21]. ATP-mediated stimulation of *ex vivo* vagal afferent sensory C-fibres from the lungs of guinea pigs is blocked by P2X3 antagonist [22]. And in human subjects with chronic refractory cough, a phase 2 study has shown a striking reduction in daily cough frequency with the P2X3/P2X2 receptor antagonist gefapixant (formerly AF-219) [23]. This represents a potential significant breakthrough in treating refractory chronic cough with a novel class of drug. Phase 3 trials of gefapixant and other P2X3 antagonists are currently in progress [24], and this class of treatments could potentially revolutionise management of an under-served group of patients.

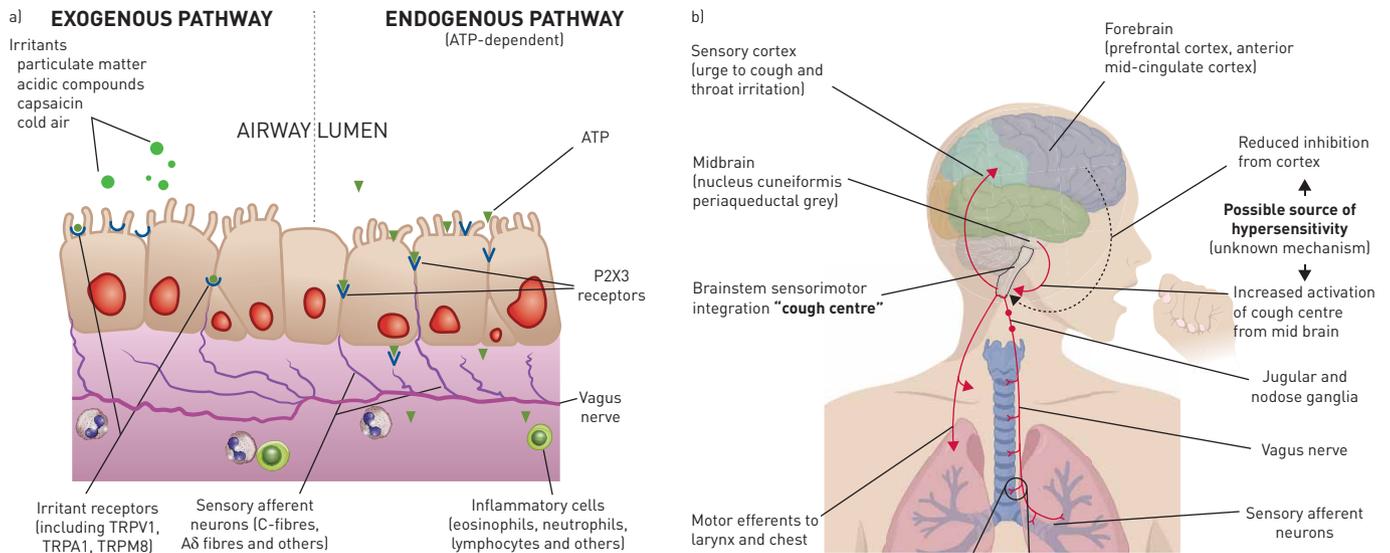
Extrapolating from the guinea pig model, the mode of action of gefapixant in humans is assumed to be through action on ATP-mediated activation of afferent nerves in the airway. Until now this assumption has not been explored, but in the current issue of the *European Respiratory Journal* MORICE *et al.* [25] address this deficiency in our knowledge. The authors report the results of a phase 2 randomised placebo-controlled study on the effects of gefapixant on tussive responses to inhaled capsaicin, citric acid, ATP and distilled water in 24 patients with chronic refractory cough and 12 healthy controls. Gefapixant failed to significantly moderate cough responses to capsaicin and citric acid, but had a substantial impact on raising the dose of ATP required to provoke the pre-specified number of coughs both in patients and, to a lesser extent, in healthy subjects. A similar, but less pronounced, effect of the drug was observed in patients on cough responses to inhaled distilled water.

This is a small single dose study, and tachyphylaxis and interaction of cough responses following repeated exposure to different inhaled tussive agents during multiple cough challenges over a short time period is a potential methodological concern. However, the sequence of administration of agents was randomised and fixed for each subject, and carried out three times with each the placebo and the active drug in a double-blinded crossover study design. Participants therefore acted as their own controls, and any tachyphylaxis might potentially diminish rather than enhance the apparent antitussive effect of gefapixant.

The findings of the current paper are a welcome contribution to our understanding of the pathophysiology of cough. This is the first study in humans to directly support a mechanism of action of gefapixant involving engagement of with the ATP receptor target. It also supports the presence of at least two distinct afferent pathways for the activation of cough (figure 1).

The tussive agents capsaicin and citric acid appear to cause cough by stimulating C-fibres and possibly A-fibres, involving TRPV1 and acid-sensing ion channels [26], and, according to the current study, independently of the ATP/P2X pathway. Although cough reflex sensitivity to capsaicin and citric acid is generally increased in patients with chronic cough [27], this probably represents a general feature of the cough hypersensitivity syndrome and a heightened response to exogenous noxious stimuli, rather than a specific mechanism in the pathogenesis of chronic refractory cough *per se*, as was previously thought. The profound antitussive effect of gefapixant in the disease, and now the demonstration specifically of its action on ATP-induced cough, strongly suggests a distinct ATP-P2X pathway in humans that could be highly relevant to mechanisms of refractory chronic cough.

So what can we conclude from recent research of gefapixant and ATP in cough? The overwhelming evidence is now for an ATP drive to chronic refractory cough, acting *via* P2X channels. What exactly drives ATP/P2X3-dependent processes though remains unclear. Could ATP be responsible for, or directly involved in the mechanism of cough hypersensitivity? In our opinion, probably no. A unique hypersensitivity to ATP seems unlikely, given that another recent observation of A.H. Morice and



**FIGURE 1** Proposed peripheral and central neural pathways in chronic refractory cough and the cough hypersensitivity syndrome. a) The periphery. Vagus nerve is stimulated by afferent nerve terminals in the airway *via* two main complementary pathways. 1) The exogenous pathway. Triggered predominantly by physical and chemical stimuli originating external to the lung, e.g. particulate matter from the air and aspirated food fragments, cold air, acids. Involves receptors including TRPV1, TRPA1 and TRPM8, but probably not, at least to a large degree, P2X3. 2) The endogenous pathway. Triggered by ATP originating from within the lung itself (possibly in response to inflammation or other causes of tissue stress). ATP interacts with P2X3, and possibly other P2X receptors. By this model experimentally inhaled tussigens cause cough predominantly by the exogenous pathway, apart from ATP which directly triggers the endogenous pathway. The P2X3 antagonist gefapixant reduces cough responses to inhaled ATP but not to inhaled citric acid or capsaicin [25]. TRPV1 antagonist reduces tussive response to inhaled capsaicin [17]. In chronic refractory cough the endogenous pathway is probably of greater importance; gefapixant, but not TRPV1 or TRPA1 antagonists, reduces daily cough frequency [17, 18, 23]. There may be overlap between the two pathways (not shown) with hypo-osmolar solutions, for example, both directly stimulating peripheral nerves and ATP release. Peripheral mediators other than ATP may also be involved in the endogenous pathway (not shown). b) Central cough pathways. Vagus nerve synapses with neurones within the medullary “cough centre” within the nucleus tractus solitarius. This in turn triggers coughing *via* motor efferents to the larynx, diaphragm and intercostal muscles. The cough centre is stimulated excessively in chronic refractory cough by higher centres, including the nucleus cuneiformis and periaqueductal grey of the midbrain [7]. Simultaneously, normal cortical inhibitory influences [e.g. from within the prefrontal cortex and anterior midcingulate cortex [7]] are diminished. These pathways are possibly responsible for cough hypersensitivity. Consequently, only low levels of exogenous stimuli *via* peripheral nociceptors, or even physiological concentrations of ATP *via* the endogenous peripheral pathway can cause cough. Modulation of sensory processing at the level of vagus nerve ganglia may also be highly relevant (not shown). Cortical pathways also involve the urge to cough and conscious sensations of coughing.

co-workers was that cough responses to inhaled ATP are no more exaggerated in refractory chronic cough than they are to other inhaled irritants [28]. Furthermore, ATP appears not to act as a general sensitiser of nerves, given that gefapixant's blockade of ATP/P2X failed to modify responses to citric acid and capsaicin in the current study [25].

This therefore leads us to the conclusion that P2X-related increased cough frequency in chronic cough may relate to an increased release or reduced breakdown of ATP in the extracellular fluid of the airway, rather than directly to hypersensitivity. The cause of hypothetically raised ATP levels in chronic refractory cough though is unspecified at present but may, at least in some cases, relate to inflammation or epithelial damage [20].

Recent work in a conscious guinea pig model suggests that TRPV4 and pannexin channels has a role in ATP release, firing of airway A $\delta$ -fibres, vagus nerve stimulation and cough, triggered by hypo-osmolar solutions applied to the airway and TRPV4 ligand, and blocked by P2X3 inhibitor [25]. This may be an analogous process to the observations involving inhaled distilled water in the current study, acting *via* ATP-dependent mechanisms [25]. However, TRPV4 seems not to be necessary for refractory chronic cough in humans, as preliminary data from a clinical trial suggest that blocking this receptor has no effect on cough frequency [29]. There is also the possibility that action of ATP outside the airways is relevant; P2X channels are anatomically widespread, and the gustatory side-effect of gefapixant clearly demonstrates that the action of the drug is not limited to the human lung [23].

Based on the current paper and prior knowledge, increased coughing in chronic refractory cough may therefore relate to a combination of three processes: 1) increased activation of afferent neurons in response to inhaled physical or chemical irritants *via* an “exogenous” peripheral pathway, independent of P2X3/

ATP, but involving TRPV1, TRPA1, TRPM8 and other receptors; 2) activation of sensory afferents by ATP which originates from within the lung itself due to inflammation and other undefined processes, acting *via* P2X receptors in an “endogenous” peripheral pathway causing increased basal cough frequency independent of direct external stimulation; and 3) cough hypersensitivity, the cause of which is yet to be identified, but could involve other peripheral and/or central processes, which reduces the threshold for activation of the cough reflex in response to afferent stimuli. This idea is illustrated in figure 1.

This model would explain why a significant minority of patients with refractory cough seem not to respond to P2X blockade, particularly those with lower daily cough frequencies [30]. Perhaps the cough of these individuals is driven predominantly by hypersensitivity and continued exposure to inhaled irritant, *e. g.* air pollution or gastro-oesophageal refluxate, rather than by endogenous ATP-dependent mechanisms. Similarly, the existence of more than one pathway to increased coughing would explain why gefapixant appears not to abolish excessive cough completely [31].

The current study therefore furthers our understanding of ATP-mediated pathways in chronic cough, even if the source of hypersensitivity remains to be defined. It is becoming increasingly clear that there is substantial heterogeneity among patients with chronic refractory cough [32, 33]. In conjunction with ongoing clinical and preclinical studies, accurate phenotyping of such patients through accurate measurement of clinical variables is key to better appreciating this heterogeneity, to predict which of a number of potential peripherally or centrally acting treatments might have the highest efficacy in each case, and to further advance understanding of chronic refractory cough [34, 35].

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