found evidence of increased airway symptoms in the latter group only.[20] A recent large study from the UK[21] failed to document any effects of VOCs on persistent wheezing illness in school children at total VOC concentrations that were higher than in the study by Rumchev *et al*, but a study from Leipzig found that early life exposure to low concentrations of 25 selected VOCs related to house painting was associated with increased respiratory infections in infants.[22] Other studies have suggested that VOC emissions from recent house redecorations and floorings might be related to asthma-like symptoms.[23 24] Whether such associations reflect direct effects of indoor VOCs at low concentrations or, for example, confounding by traffic related pollutants covarying with indoor VOCs[25] remains to be seen.

The issue of whether indoor VOCs are a risk factor for asthma in children therefore seems still to be largely undecided. In view of the methodological difficulties outlined above, prospective studies are more likely to produce progress in deciding whether we need to worry about indoor VOCs as determinants of asthma at the relatively low concentrations typically encountered in the home environment.

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REFERENCES

1 **Lau S**, Illi S, Sommerfeld C, *et al.* Early exposure to house-dust mite and cat allergens and development of childhood asthma: a cohort study. Multicentre Allergy Study Group. *Lancet* 2000;**356**:1392–7.
2 **Wahn U**, Lau S, Bergmann R, *et al.* Indoor allergen exposure is a risk factor for sensitization during the first three years of life. *J Allergy Clin Immunol* 1997;**99**:763–9.
3 **Almqvist C**, Egmar AC, Hedlin G, *et al.* Direct and indirect exposure to pets—risk of sensitization and asthma at 4 years in a birth cohort. *Clin Exp Allergy* 2003;**33**:1190–7.
4 **Anyo G**, Brunekreef B, de Meer G, *et al.* Early, current and past pet ownership: associations with sensitization, bronchial responsiveness and allergic symptoms in school children. *Clin Exp Allergy* 2002;**32**:361–6.
5 **de Meer G**, Toelle BG, Ng K, *et al.* Presence and timing of cat ownership by age 18 and the effect on atopy and asthma at age 28. *J Allergy Clin Immunol* 2004;**113**:433–8.
6 **Oryszczyn MP**, Annesi-Maesano I, Charpin D, *et al.* Allergy markers in adults in relation to the timing of pet exposure: the EGEA study. *Allergy* 2003;**58**:1136–43.
7 **Svanes C**, Heinrich J, Jarvis D, *et al.* Pet-keeping in childhood and adult asthma and hay fever: European community respiratory health survey. *J Allergy Clin Immunol* 2003;**112**:289–300.
8 **Phoa LL**, Toelle BG, Ng K, *et al.* Effects of gas and other fume emitting heaters on the development of asthma during childhood. *Thorax* 2004;**59**:741–5.
9 **Rumchev K**, Spickett J, Bulsara M, *et al.* Association of domestic exposure to volatile organic compounds with asthma in young children. *Thorax* 2004;**59**:746–51.
10 **Cooper KR**, Alberti RR. Effect of kerosene heater emissions on indoor air quality and pulmonary function. *Am Rev Respir Dis* 1984;**129**:629–31.
11 **Triche EW**, Belanger K, Beckett W, *et al.* Infant respiratory symptoms associated with indoor heating sources. *Am J Respir Crit Care Med* 2002;**166**:1105–11.
12 **Maier WC**, Arrighi HM, Morray B, *et al.* Indoor risk factors for asthma and wheezing among Seattle school children. *Environ Health Perspect* 1997;**105**:208–14.
13 **Ponsonby AL**, Couper D, Dwyer T, *et al.* The relation between infant indoor environment and subsequent asthma. *Epidemiology* 2000;**11**:128–35.
14 **Kilpelainen M**, Koskenvuo M, Helenius H, *et al.* Wood stove heating, asthma and allergies. *Respir Med* 2001;**95**:911–6.
15 **Morris K**, Morgenlander M, Coulehan JL, *et al.* Wood-burning stoves and lower respiratory tract infection in American Indian children. *Am J Dis Child* 1990;**144**:105–8.
16 **Ostro BD**, Lipsett MJ, Mann JK, *et al.* Indoor air pollution and asthma. Results from a panel study. *Am J Respir Crit Care Med* 1994;**149**:1400–6.
17 **Molhave L**. Indoor climate, air pollution, and human comfort. *J Expos Anal Environ Epidemiol* 1991;**1**:63–81.
18 **Hudnell HK**, Otto DA, House DE, *et al.* Exposure of humans to a volatile organic mixture. II. Sensory. *Arch Environ Health* 1992;**47**:31–8.
19 **Kogevinas M**, Anto JM, Sunyer J, *et al.* Occupational asthma in Europe and other industrialised areas: a population-based study. European Community Respiratory Health Survey Study Group. *Lancet* 1999;**353**:1750–4.
20 **Wieslander G**, Norback D, Edling C. Airway symptoms among house painters in relation to exposure to volatile organic compounds (VOCs)—a longitudinal study. *Ann Occup Hyg* 1997;**41**:155–66.
21 **Venn AJ**, Cooper M, Antoniak M, *et al.* Effects of volatile organic compounds, damp, and other environmental exposures in the home on wheezing illness in children. *Thorax* 2003;**58**:955–60.
22 **Diez U**, Kroessner T, Rehwagen M, *et al.* Effects of indoor painting and smoking on airway symptoms in atopy risk children in the first year of life results of the LARS-study. Leipzig Allergy High-Risk Children Study. *Int J Hyg Environ Health* 2000;**203**:23–8.
23 **Jaakkola JJ**, Parise H, Kislitsin V, *et al.* Asthma, wheezing, and allergies in Russian schoolchildren in relation to new surface materials in the home. *Am J Public Health* 2004;**94**:560–2.
24 **Jaakkola JJ**, Oie L, Nafstad P, *et al.* Interior surface materials in the home and the development of bronchial obstruction in young children in Oslo, Norway. *Am J Public Health* 1999;**89**:188–92.
25 **Delfino RJ**, Gong H, Linn WS, *et al.* Respiratory symptoms and peak expiratory flow in children with asthma in relation to volatile organic compounds in exhaled breath and ambient air. *J Expos Anal Environ Epidemiol* 2003;**13**:348–63.

TRPV1 and cough

G P Anderson

Iodo-resiniferatoxin, a new TRPV1 inhibitor, shows promising antitussive activity in an animal model

Cough is one of the most common respiratory complaints and intractable cough remains one of the most distressing and difficult to treat conditions of the lung. It is ironical that the billions of dollars spent worldwide on proprietary over the counter remedies of questionable efficacy[1] for cough exceeds, by orders of magnitude, the money spent on basic cough research. It is therefore not surprising that the cough pharmacopoeia has altered little in the last 50 years, with no important advances over opiate based compounds and cromones. However, basic researchers have not been idle. In this issue of *Thorax* Trevisani and colleagues[2] present new information pointing to a causative role for an ion channel called transient receptor potential vanilloid-1 (TRPV1) in cough. They show that the highly selective and potent TRPV1 inhibitor iodo-resiniferatoxin, derived from a plant toxin found in *Euphorbia* species, strongly suppresses cough induced by inhaled capsaicin or citric acid in conscious guinea pigs, a widely used animal cough model.

The basis of this work is careful molecular dissection of precisely why coughing occurs when irritants are inhaled. It has been known for years that irritants such as citric acid and capsaicin (the pungent tongue burning constituent of hot chilli peppers) trigger coughing. It has also been known for decades from electrophysiological studies that such irritants activate respiratory tract sensory fibres—especially unmyelinated C fibres—to discharge information via the vagus to the medullary cough centre.[3] From this early work it was inferred that the cough receptor on sensory fibres might be an ion channel able to rapidly depolarise afferent nerve membranes and hence trigger cough inducing impulses. This view was reinforced by the inhibitory activity of crude agents such as the dye ruthenium red. The discovery that capsazepine, a capsaicin derivative and a known ion channel blocker, had antitussive activity in animal models[4] focused attention on the vanilloid receptor family as candidate ion channels.

The TRPV1 channel is a so-called receptor operated ion channel. It is moulded from six transmembrane domains that cluster forming a molecular ''gate'' which regulates the flow of cations across membranes when activated by a soluble ligand. TRPV1 is encoded on chromosome 17p13.3 and is also known as the capsaicin receptor, and the vanilloid receptor subtype 1 (VR1). This channel has been of interest to pain researchers for some time as it is known that the TRPV1 channel can be activated by painful heat (>43˚C) and acid (pH <6.5). Its expression, however, is not confined to sensory nerves; TRPV1 has also recently been found on glial cells, endothelium, epithelium and keratinoctyes, suggesting that it may have a much broader role in regulating responses to tissue injury. Indeed, as there is no good evolutionary reason why the lower lung should respond to hot pepper extracts, it has been strongly suspected that there must be one or more endogenous ligands for TRPV1. To date, three putative ''endovanilloids'' including N-acyldopamines, arachidonic acid lipoxygenase metabolites, and anandamide (the endogenous ligand for cannabis receptors) have been identified.[5] It is quite conceivable that these endoligands may be upregulated—together with kinins, histamine, and other known cough triggers—in lung diseases, but their specific relationship to cough is unknown.

TRPV1 therefore has the attraction of being a common activation point for coughing induced by different stimuli. As always, there are caveats. The cough reflex has important survival benefits and it is likely that multiple cough pathways have co-evolved. Mice breathe too rapidly and too shallowly to generate the airflow turbulence necessary to clear mucus by coughing, but they have a highly conserved afferent fibre TRPV1 which has strong homology with the human form. Elegant research by Kollarik and Undem[6] has very recently identified TRPV1 independent discharges in bronchopulmonary vagal afferent fibres to bradykinin and acid in TRPV1 knock-out mice, indicating that at least one ''back up'' mechanism must exist. These findings are consistent with earlier studies showing that capsazepine did not block all cough inducing stimuli.[4] It is also clear that patients with chronic cough have a reduced threshold for stimulation of cough, most probably because their afferent sensory fibres have become sensitised in a manner analogous to hyperalgesia in chronic pain. It is thought that this sensitisation may have both a peripheral and a CNS component. The role of TRPV1 in the induction or reversal of sensitisation—which may underlie very intractable cough—remains unknown. Moreover, the causes of cough in humans range from the physiological to the existential. While it is reasonable to hope that TRPV1 targeted treatments might benefit cough in very common clinical settings such as chronic obstructive pulmonary disease, post-viral cough syndromes, and cough associated with gastro-oesophageal reflux disease, it seems unlikely that the concept would benefit ''psychogenic'' cough at all.

Notwithstanding these limitations, the work of Trevisani and coworkers showing a therapeutic benefit of inhibiting TRPV1 with iodo-resiniferatoxin (and the more than 60 patents already filed in this field) suggests that there may soon be safer and more effective agents to deal with this perennial problem.

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REFERENCES

1 **Schroeder K**, Fahey T, Over-the-counter medications for acute cough in children and adults in ambulatory settings (Cochrane Review). In: *The Cochrane Library*. Chichester: John Wiley & Sons, 2004.
2 **Trevisani M**, Milan A, Gatti R, *et al*. Antitussive activity of iodo-resiniferatoxin in guinea pigs. *Thorax* 2004;**59**:769–72.
3 **Coleridge JC**, Coleridge HM. Lower respiratory tract afferents stimulated by inhaled irritants. *Am Rev Respir Dis* 1985;**131**:S51–4.
4 **Lalloo UG**, *et al*. Capsazepine inhibits cough induced by capsaicin and citric acid but not by hypertonic saline in guinea pigs. *J Appl Physiol* 1995;**79**:1082–7.
5 **Van Der Stelt M**, Di Marzo V. Endovanilloids. Putative endogenous ligands of transient receptor potential vanilloid 1 channels. *Eur J Biochem* 2004;**271**:1827–34.
6 **Kollarik M**, Undem BJ. Activation of bronchopulmonary vagal afferent nerves with bradykinin, acid and vanilloid receptor agonists in wild-type and TRPV1-/- mice. *J Physiol* 2004;**555**(Pt 1):115–23.

Pneumocystis jirovecii infection

R Miller, L Huang

A review of *Pneumocystis* and the rationale for renaming it

The organism *Pneumocystis* causes severe pneumonia in individuals with immune systems impaired by HIV, transplantation, malignancy, connective tissue disease, and the treatment thereof. In HIV infected patients it remains a major pathogen in those who are unaware of their HIV serostatus, or who decline to take or are intolerant of highly active antiretroviral therapy. *Pneumocystis* also infects a wide variety of mammals and causes pneumonia in those that are immunosuppressed or immunodeficient. Originally *Pneumocystis* was thought to be a single species of protozoa. Study of the organism has been severely hampered by the fact that it cannot be cultured in vitro. Over the last 20 years, using molecular biological, immunological and other techniques, *Pneumocystis* has been shown to be a fungus, to be genetically diverse, host species specific, transmissible from animal to animal, to colonise individuals with minor degrees of immunosuppression, and to cause clinical disease by ''new'' infection in addition to reactivation of latent childhood acquired infection. More recently the organism causing disease in humans has been renamed *Pneumocystis jirovecii*. This article highlights some of these recent developments and provides a rationale for the renaming of the organism.

WHAT IS *PNEUMOCYSTIS*?

Chagas first identified *Pneumocystis* organisms in humans in 1909, but they were mistaken for a new stage of the life cycle of the protozoan *Trypanosoma cruzi*.[1] Within a very short time it became apparent that the organism infected other host species, was not a trypanosome, and was named