PERSPECTIVES

TRPA1: irritant detector of the airways

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The respiratory tract is innervated by primary afferent sensory neurons that respond to mechanical and chemical stimuli (Taylor-Clark & Undem, 2006). The majority of these neurons are unmyelinated C-fibres that respond to noxious chemicals, such as reactive oxygen species (ROS), the main irritants of tear gas, air pollution and burning vegetation (Kollarik & Undem, 2004). Activation of airway sensory neurons leads to centrally mediated afferent reflexes including shortness of breath, cough and changes in breathing patterns. Sensory neuron activation also triggers the local release of inflammatory mediators that sensitize the airways to future chemical and mechanical stimuli. While normally protective, airway inflammation can exacerbate respiratory disorders such as asthma, emphysema or bronchitis. In this issue of *The Journal of Physiology*, Taylor-Clark *et al.* (2008) investigate the role of the transient receptor potential (TRP) channels, TRPV1 and TRPA1, as sensors for oxidative stress in the airways.

The heat and capsaicin receptor, TRPV1, has long been thought to play a role in the detection of noxious chemicals in the airway. However, mice lacking the TRPV1 ion channel display only partial defects in nocifensive responses to inhaled irritants (Kollarik & Undem, 2004). Thus, other receptors are required for the detection of irritants by vagal neurons. The ion channel TRPA1 has now emerged as a leading candidate for an airway irritant detector.

TRPA1 is highly expressed in a subset of TRPV1-expressing primary sensory afferents and has been shown to play a key role in pain and neurogenic inflammation. TRPA1 is activated by reactive environmental irritants such as mustard oil, cinnemaldehyde and the α,β-unsaturated aldehyde, acrolein, an airway irritant present in tear gas, vehicle exhaust and smoke (Jordt & Ehrlich, 2007). Recent studies have identified a number of reactive endogenous molecules that activate TRPA1 including 4-HNE, 4-HHE and 4-ONE, products of oxidative stress-induced lipid peroxidation (Macpherson *et al.* 2007; Trevisani *et al.* 2007; Andersson *et al.* 2008).

Taylor-Clark *et al.* (2008) use a variety of techniques to examine the role of TRPA1 in the airways. Using calcium imaging they show that cultured vagal neurons innervating the respiratory tract are potently activated by the lipid peroxidation product 4-ONE. At lower concentrations of 4-ONE, calcium responses are absent in neuronal cultures generated from TRPA1-deficient mice. However, at higher concentrations, 4-ONE elicits robust calcium influx in TRPA1-deficient neurons; these responses are attenuated in TRPV1-deficient neurons. These results suggest that both TRPA1 and TRPV1 contribute to cellular sensitivity of lipid peroxidation products. Further analysis of the relative contributions of these channels to 4-ONE sensitivity must await the characterization of neurons from animals lacking both TRPV1 and TRPA1.

To address the role of TRPA1 in the airways *in situ*, Taylor-Clark *et al.* measure the effects of lipid peroxidation products on contractions of isolated bronchi. They find that 4-ONE induces robust bronchi contraction via sensory neuron-mediated release of neuropeptides. Strikingly, 4-HNE had little effect on bronchi contraction. The authors also use an *ex vivo* vagally innervated lung preparation to record action potential discharge in response to irritant application. While 4-ONE robustly evoked action potential discharge, 4-HNE had no effect on fibre firing. Responses to 4-ONE were not observed in lung preparations isolated from TRPA1-deficient mice, demonstrating that TRPA1 is required for 4-ONE airway sensitivity.

It is surprising that 4-HNE has little effect on bronchi contraction or action potential firing in lung afferents, as this chemical robustly stimulates calcium influx through TRPA1 in cultured sensory neurons and TRPA1-transfected cell lines (MacPherson *et al.* 2007; Trevisani *et al.* 2007; Andersson *et al.* 2008; Taylor-Clark *et al.* 2008). Also, 4-HNE was shown to elicit robust TRPA1-dependent nocifensive behaviour when injected subcutaneously into the hindpaw of mice (Trevisani *et al.* 2007). This suggests that TRPA1 sensitivity to irritants may differ depending on the tissue environment. In addition, tissue-specific signalling pathways may differentially modulate sensory neuron excitability in response to ROS.

Taken together these findings suggest that TRPA1 activation by 4-ONE is a key mechanism that links oxidative stress to nocifensive responses in the airway. A recent study by Bessac *et al.* (2008) also probes the role of TRPA1 in airway irritancy. Their study demonstrates that TRPA1 is required for nocifensive airway responses to the reactive oxygen species, hydrogen peroxide. Individuals with altered respiratory function display hypersensitivity to environmental irritants that robustly activate TRPA1. Thus, TRPA1 may represent a new target for the development of drugs that suppress neuronal hypersensitivity in individuals with airway disease.

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