The Role of TRPA1 and TRPV1 in Tussive Responses to PGE$_2$, Bradykinin and Low pH

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Excessive cough is a common medical complaint, which is often associated with inflammatory airway disease, but can also be idiopathic. Prostaglandin E$_2$ (PGE$_2$), bradykinin (BK) and an acidic environment are often present in the inflamed lung. Exposure to aerosol of these mediators can cause cough in man, suggesting they play central roles in excessive cough. To attenuate these tussive agents independently would require multiple therapies and may remove their beneficial effects e.g. PGE$_2$ is protective in the asthmatic airway. We hypothesise that these endogenous tussive agents may activate a common signalling pathway which may be targeted effectively by anti-tussive agents. Activation of TRPA1 and TRPV1 on sensory nerves depolarises vagal nerves and induces cough. Our aim was to determine the role of TRPA1 and TRPV1 in PGE$_2$, BK and low pH-induced sensory nerve activation and cough.

PGE$_2$, BK or low pH caused depolarisation of isolated guinea-pig and mouse vagal sensory nerves, and induced coughing in conscious guinea-pigs. To study the role of TRPA1 and TRPV1 ion channels in the response to these tussive agents we used selective antagonists, and vagal tissue from Trpa1$^{-/-}$ or Trpv1$^{-/-}$ mice. Cough and vagus nerve responses to PGE$_2$ and BK stimulation were partially mediated by either TRPA1 or TRPV1, and responses were abolished with a combination of both antagonists. In contrast, vagus nerve responses to low pH were partially mediated by TRPV1 or a general ASIC channel inhibitor, and responses were abolished with a combination of both antagonists. Whereas, guinea-pig cough was partially mediated by either TRPA1 or TRPV1; but coughing was still evident with a combination of both TRPA1 and TRPV1 antagonists, still leaving a possible role for ASIC channels in vivo.

In summary, both TRPA1 and TRPV1 play central roles in PGE$_2$ and BK sensory nerve activation and cough. Whereas, low pH activates sensory nerves through TRPV1 and ASIC channels, but TRPA1 may still play a role in low pH-induced cough in vivo. This data suggests that TRPA1 and TRPV1 channels would make attractive targets to treat excessive cough.

**Figure 1.** Inhibition of guinea-pig cough responses to PGE$_2$, BK and Low pH injected i.p. with TRPA1 (A1) or TRPV1 (V1) selective antagonists or appropriate vehicle (Veh). Agonists were aerosolised for 10 min, during which time the number of coughs were counted. * indicates significance (p < 0.05) compared with vehicle control, analysed by Kruskal Wallis one-way ANOVA with Dunn’s post-hoc test.