TRPV1 polymorphisms influence capsaicin cough sensitivity in men

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Introduction

Capsaicin, the hot component of chilli peppers, is a well-known tussive agent, which is regularly used as a tool to study cough and antitussives (1). Capsaicin is known to activate the transient receptor potential vanilloid 1 (TRPV1) cation channel which is thought to be involved in pain perception, inflammation, itch and cough (2-4). These functions within the body make TRPV1 an exciting target for research and drug development.

As with many of the TRP channels, TRPV1 has naturally occurring polymorphisms, most of which are conservative substitutions (approximately 70%). Naturally occurring genetic variations of the channel may account for individual differences in conditions where TRPV1 is important. Indeed, initial studies investigating the possible association between TRP channels and human health and disease have so far shown a role for TRPV1. In a case-controlled study investigating 149 polymorphisms from 14 TRP channels, SNPs in TRPV1 and TRPV3 showed association with migraines in the Spanish population (5). In cough and airway diseases, the presence of the polymorphism TRPV1-I585V was recently found to be associated with a significantly reduced risk of cough in asthmatic children (6). Another case-controlled study investigated the association between TRP SNPs, irritant exposure and cough. The group found that TRPV1 polymorphisms were associated with non-asthmatic cough and that cough symptoms were worsened by exposure to irritants (7). Interestingly, in this study the group also found an association between the polymorphism TRPV1-I585V and a lower risk of nocturnal cough in asthmatic adults but only in one of their patient cohorts, not across the entire population (7). The literature suggests that TRPV1 genetic variation is important in human health and disease, especially in cough. In addition the polymorphism I585V has been highlighted as important for cough sensitivity.

The aim of the present study was to identify whether polymorphisms of the TRPV1 channel are important in determining capsaicin cough challenge sensitivity. Human volunteers were therefore given a capsaicin cough challenge and blood samples were taken for genetic analysis of the TRPV1 gene to determine whether there were any significant associations.

Methods

For this study we sought volunteers who were insensitive to chilli, by a local public appeal. Four subjects claiming to be insensitive to hot curries responded. These male volunteers were administered capsaicin cough challenges in accordance with the European Respiratory Society guidelines (8). The concentration of capsaicin causing two (C2) or five (C5) coughs were recorded.

As Capsaicin is known to activate TRPV1 (2) we extracted genomic DNA from blood using a Qiagen DNA Blood mini kit and sequenced the TRPV1 gene to identify polymorphisms, as described previously (6).

In order to determine the effect that the polymorphisms had on TRPV1 activity, we then performed functional studies. HeLa cells were transiently transfected with the wild type TRPV1, the triple mutant TRPV1-I315-I469-V585 and the single mutant TRPV1-V585 as described previously (6). Calcium signalling experiments were used to assess channel activity using capsaicin as an agonist. Cells were loaded with fura-2AM as described previously (6) and changes in cytosolic calcium were expressed as the ration of emitted fluorescence at 510 nm after excitation at both 340 and 380 nm.

Table 1 Capsaicin concentrations required to evoke two (C2) and five (C5) coughs in male control subjects and those claiming to be chilli insensitive

	Control population (males) (n=13)	Chilli insensitive (n=4)
C2 (μM)	34.5	>1,000
C5 (μM)	77.2	>1,000

Results

All four chilli insensitive individuals displayed reduced capsaicin sensitivity with three out of four failing to cough at least twice at the top dose of 1 mM (*Table 1*).

Sequencing of their TRPV1 gene revealed that all capsaicin insensitive individuals carried the TRPV1-V585 mutation and the triple mutations TRPV1-I315-I469-V585, but the male control population had a distribution of TRPV1 polymorphisms similar to the 1,000 genomes project data (British population).

Calcium signalling experiments using TRPV1 heterologously expressed in HeLa cells showed a similar rightward shift in the capsaicin concentration effect curve in the TRPV1-I315-I469-V585 and TRPV1-V585 variant channels compared to the wild type TRPV1-I585 channel (data not shown). This suggests that *in vitro* diminished capsaicin sensitivity was due to the TRPV1-V585 mutation alone.

Discussion

Male volunteers claiming to be insensitive to chilli showed a large increase in capsaicin cough challenge threshold. Indeed three out of four failed to cough at least twice to the top dose of capsaicin. Analysis of their TRPV1 gene demonstrated that all four subjects carried the TRPV1-V585 variant rather than the TRPV1-I585 wild type channel, yet a male control population had a distribution of TRPV1-585 polymorphisms similar to the 1,000 genomes project data (British population). In agreement with published literature, functional studies using cells heterologously expressing TRPV1 also showed reduced capsaicin sensitivity in the TRPV1-V585 variant compared to the wild type channel (6). We therefore suggest that in men TRPV1-V585 may endow insensitivity to irritant stimuli in the airways.

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Footnote

Conflict of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: NRES committee Yorkshire and the Humber – Humber Bridge research ethical approval reference number 07/H1304/99.

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