Human ACE gene polymorphism and distilled water induced cough

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Abstract

Background — Inhibitors of angiotensin converting enzyme (ACE) cause a non-productive cough. The insertion/deletion polymorphism of ACE was used as a genetic marker to investigate the relationship between ACE genotype and cough sensitivity.

Methods — A double blind cough challenge was performed in 66 normotensive subjects (34 men) of mean age 34.8 years (range 18–80) using aerosols of distilled water. The number of coughs during the one minute exposure to water was recorded. DNA samples from venous blood were amplified by the polymerase chain reaction and resolved on a 1% agarose gel. They were analysed for the presence of a polymorphism in intron 16 of the ACE gene consisting of an insertion (I) or deletion (D) of an Alu repetitive sequence 287 base pairs long.

Results — The distribution of genotypes was 20 II, 26 ID, and 20 DD. The cough response was significantly (p<0.01) related to the ACE genotype, the mean number of coughs being 15.8, 11.3, and 9.6, respectively, in subjects with the II, ID, and DD genotypes.

Conclusions — The observation that cough challenge is dependent on ACE genotype in normal subjects is evidence of a link between ACE activity and the cough reflex.

(Thorax 1997;52:111–113)

Keywords: DNA polymorphism, cough, angiotensin converting enzyme.
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genotypes were 15.8 (range 1–28) and 9.6 (range 0–22) respectively; p<0.01. The mean number of coughs for subjects of the ID genotype was 11.3 (range 0–27). Individual data with 95% confidence intervals are shown in fig 1.

### Discussion

The involvement of ACE in the human cough reflex was revealed by the development of a dry cough in up to 15% of patients receiving treatment with ACE inhibitors. This side effect occurs with compounds of differing chemical structure and is therefore likely to be due to the inhibition of ACE activity rather than to any idiosyncratic reaction. In vivo, ACE is capable of metabolising several small peptides including substance P and bradykinin. We have previously shown that ACE inhibition causes a change in the concentration-response relationship to tussive challenge with capsaicin and have hypothesised that an increase in the perineuronal concentration of substance P underlies the increased cough sensitivity which occurs in ACE inhibitor cough. Indeed, increased levels of substance P are found in the sputum of patients with ACE inhibitor cough.

The cough produced by hypotonic solutions has been extensively studied and is characterised by rapid tachyphylaxis. The number of coughs produced per minute is proportional to the concentration of chloride in the nebulised solution, an observation which has been ascribed to the lack of a “permeant anion” since replacement of chloride by acetate or bicarbonate still leads to coughing. Hypotonic solutions presumably alter the ionic composition of the airway surface liquid and extracellular fluid in adjacent paracellular spaces causing discharge of the putative cough receptor. Airways surface liquid is the inner serious fluid lining the trachea and bronchi and consists of a layer 15–30μm thick with a chloride content of approximately 80 mmol/l. The hypotonic composition of this layer is governed by active transport of ions – particularly the inward transport of sodium – by epithelial cells. Inhalation of distilled water may be expected to reduce the chloride content of airways surface liquid further.

Human somatic ACE is an extensively glycosylated protein of 170 kilodaltons which is uniquely reliant on monovalent anions, particularly chloride, for activity. We hypothesised that cough produced by distilled water was caused by a local inhibition of ACE activity resulting from a reduction of chloride concentration in the airway surface liquid, and that subjects with genetically determined low ACE levels would therefore be more susceptible to cough produced by distilled water. Our results show that those subjects known to exhibit lower ACE activity (II genotype) have a significantly greater cough response than those of the DD genotype.

Surprisingly, there is no obvious relationship between ACE inhibitor cough and the ACE gene polymorphism in Caucasian subjects. Treatment with ACE inhibitors leads to a
slowly developing but marked reduction of ACE activity which may be compensated by an increase in activity of other peptide degrading pathways. One such pathway is as neutral endopeptidase (NEP) which has been shown to regulate both substance P metabolism and cough in animal models. Patients with ACE inhibitor cough may thus be deficient in this alternative pathway of degradation of pro-tussive peptides rather than in basal ACE activity.

In summary, we have shown an increased sensitivity of the cough reflex to stimulation with distilled water in subjects with the II genotype of ACE polymorphism. The link between ACE activity and cough sensitivity supports a physiological role for ACE in the cough reflex in man.

AJT was supported by the Medical Research Council

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Thorax 1997 52: 111-113
doi: 10.1136/thx.52.2.111

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