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ORIGINAL ARTICLE

# Differences between zofenopril and ramipril, two ACE inhibitors, on cough induced by citric acid in guinea pigs: role of bradykinin and PGE2

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**Abstract** Dry and persistent cough is one of the commonest side effects experienced by patients treated with angiotensin-converting enzyme (ACE) inhibitors for the therapy of hypertension and congestive heart failure. The present study investigated the effect of zofenopril and ramipril on cough induced by citric acid in guinea pig and the involvement of bradykinin (BK) and prostaglandin E2 (PGE2) in mediating the responses of these drugs. Zofenopril (10 mg/kg) or ramipril (3–10 mg/kg), which is threefold more potent than zofenopril, on a mg basis, in lowering blood pressure, was orally administered daily in drinking water for 2 weeks. At the end of this period, aerosol of citric acid solution (0.1 M) was performed and the number of cough counted for 10 min. The role of the kinin $B_2$ receptor was also investigated. BK and PGE2 levels in the bronchoalveolar lavage (BAL) fluid were measured after repeated oral treatment with zofenopril or ramipril (10 mg/kg). Ramipril (3–10 mg/kg) increased citric acid-induced cough by 40% and 60%, respectively, as compared to the vehicle control group (15.0±1.8), while zofenopril (10 mg/kg) was without effect. The enhancement of citric acid-induced cough caused by ramipril (10 mg/kg) was reduced by the kinin $B_2$ receptor antagonist MEN16132 (0.25 mg/kg ip). BK and PGE2 levels in the BAL fluid were increased, in comparison to the control group, after ramipril treatment, while they were unchanged after zofenopril administration. Zofenopril, contrary to ramipril, did not affect either citric acid-induced cough in the guinea pigs or BK and PGE2 production in the airways.

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**Keywords** Zofenopril · Ramipril · Cough · Citric acid · Bradykinin · PGE2

## Introduction

Angiotensin-converting enzyme (ACE) inhibitors are drugs widely used for the treatment of cardiovascular diseases such as hypertension, congestive heart failure, and myocardial infarction.

ACE, or kininase II, is a bivalent dipeptidyl carboxyl metallopeptidase which cleaves the C-terminal dipeptide from different peptides including Angiotensin I, bradykinin (BK), and substance P (SP) leading to the production of the potent vasopressor peptide angiotensin II and to the degradation of the vasodepressor peptide bradykinin (Brown and Vaughan 1998).

The beneficial cardiovascular effects of ACE inhibitors occur with the inhibition of both the renin–angiotensin system, which is involved in the blood pressure regulation, and the kallikrein-kinin system resulting in a reduced formation of Angiotensin II and a reduced degradation of BK (Linz et al. 1995; Brown and Vaughan 1998).

Despite the fact that this class of drugs is generally well tolerated, one of the most commonly experienced side effects is a persistent dry cough which affects about 5% to 20% of treated patients in the white populations, especially among women, and up to 44% in Asian populations (Israili and Hall 1992; Woo and Nicholls 1995).

The side effect of cough seems scarcely related to the activity of these drugs on the renin–angiotensin system as treatment with angiotensin receptor blockers and renin inhibitors caused a lower incidence of cough than ACE inhibitors (Pylypchuk 1998; Sleight 2009). The mechanism for ACE inhibitor-induced cough is still controversial;

however, the most accepted hypothesis is that this effect is caused by a decreased inactivation of circulating bradykinin. There is evidence that Icatibant reduced captopril-induced enhancement of cough caused by citric acid in guinea pigs showing a role of BK in the cough produced by ACE inhibitors (Fox et al. 1996). Furthermore, the susceptibility to develop cough seems to be coupled with the presence of a genetic variant of the bradykinin $B_2$ receptor promoter (Mukae et al. 2002).

Although cough is an adverse effect common to all ACE inhibitors, differences among compounds in the severity of potentiation of experimentally induced cough in guinea pigs have been shown (Takahama et al. 1993; Takahama et al. 1996) suggesting different mechanisms of action. Differences among ACE inhibitors' activity were also observed towards another BK-mediated effect such as the microvascular leakage in the guinea pig airways (Murata et al. 1995).

The most common ACE inhibitors used in therapy belong to various chemical classes, and differ in potency, bioavailability, plasma half-life, route of elimination, distribution, and affinity for tissue-bound ACE and in their pharmacological characteristics as prodrugs (Brown and Vaughan 1998).

In this study, we have compared the ability of two ACE inhibitors, zofenopril and ramipril, containing in their structure a sulfhydryl group and a carboxyl moiety, respectively, in affecting citric acid-induced cough in guinea pigs, and we have also investigated the role of BK and prostaglandin E2 (PGE2) in mediating this effect. The doses of zofenopril and ramipril selected for this study have been chosen on their quantitatively comparable effects in inhibiting systolic blood pressure in spontaneous hypertensive rats (SHR; Cushman et al. 1989a). Ramipril is about threefold more potent than zofenopril in lowering blood pressure. For this reason, we have tested the doses of 3 and 10 mg/kg for ramipril and 10 mg/kg for zofenopril. We could not test the dose of 30 mg/kg of zofenopril, to compare with 10 mg/kg of ramipril, because its low solubility in water did not allow us to perform the oral administration in drinking water.

Citric acid was chosen as a cough inducer since it is a well-known nonspecific noxious stimulus which caused cough in animals (Featherstone et al. 1996) and humans (Pounsford et al. 1985).

## Methods

### Study design and ACE inhibitors' treatment

Male Dunkin Hartley guinea pigs weighing 350–400 g were housed in single cages at a constant temperature and humidity with a 12-h light/dark cycle. The experiments were performed in accordance with the principles and guidelines of the European Union regulations and the local ethical committee.

The animals were individually placed in each cage and were fed with a standard pellet diet and with water supplied from drinking bottles. After the first week in which the guinea pigs were allowed to get used to drink from the drinking bottles, the animals were divided into four groups and assigned to ACE inhibitors' treatment with zofenopril (10 mg/kg day), ramipril (3–10 mg/kg day), or water for the control group.

Zofenopril and ramipril were solubilized in drinking water for oral administration. A constant volume of the solutions, exceeding the daily amount necessary, was put in the drinking bottles and was changed every day in order to adjust the drugs' concentration to the previous day's volume intake and to the guinea pigs' body-weight variation.

ACE inhibitors' administration in the drinking water was performed for 14 days.

The doses of the two ACE inhibitors were chosen on the basis of the antihypertensive potency in inhibiting the plasma ACE (Cushman et al. 1989a, b).

The low water solubility of zofenopril did not allow us to test doses higher than 10 mg/kg/day.

### Citric acid-induced cough

At the end of the 14-day oral treatment, unanesthetized animals were placed in individual transparent perspex chambers and exposed to nebulized aqueous solution of 0.1 M citric acid for 10 min.

The aerosol was generated with a nebulizer (Pari Jet-nebulizer, Hugo Sachs Elektronik, Harvard Apparatus, Germany) driven by compressed air at a pressure of 200 kPa delivering a volume of 500 μl/min with an aerodynamic mass median diameter below 10 μm. The number of coughs was detected by a microphone placed inside the chamber and connected to a Mac Lab/8S data acquisition system (ADInstruments, UK) for tracings recording and also counted, during the 10 min of aerosol exposition, by an observer who directly checked the animals' cough responses.

A preliminary dose-response study was performed with increasing concentrations (0.1, 0.2, and 0.4 M) of citric acid in order to choose the suitable concentration causing a reproducible cough response.

### Bradykinin $B_2$ receptor antagonist treatment

In a separate experimental session, in order to investigate the role of BK in ACE inhibitor-induced cough potentiation, the

bradykinin $B_2$ receptor antagonist MEN16132 (0.25 mg/kg) was administered intraperitoneally, 30 min before the aerosol of 0.1 M citric acid solution after 14 days of ramipril (10 mg/kg/day os) treatment and in the vehicle control animals.

MEN16132 is a potent and highly selective nonpeptide BK $B_2$ receptor antagonist either in vitro (cells, isolated organs) or in vivo, after systemic or local administration, in various species. If compared to the peptide $B_2$ receptor antagonist icatibant, MEN16132 possesses similar binding affinity in several preparations but a higher antagonist potency, particularly in human and guinea pig preparations, and a slower reversibility of the $B_2$ receptor blockade. In vivo models, after iv administration, MEN16132 is at least 30-fold more potent than icatibant on bronchoconstriction induced by BK.

### Bradykinin and PGE2 metabolite levels in the BAL fluid

For the bronchoalveolar lavage (BAL) fluid collection after 14 days of oral treatment with zofenopril (10 mg/kg/day), ramipril (10 mg/kg/day), or water, guinea pigs were anesthetized with pentobarbital (40 mg/kg i.p.), a cannula was inserted into the trachea, and the airways were washed with 10 ml of PBS ($Ca^{2+}$-free) divided in three aliquots of 4, 3, and 3 ml. The fluid was centrifugated at 10,000 rpm for 10 min at 4°C and the supernatant collected for the determination of BK and PGE2 levels. Since PGE2 is rapidly metabolized in vivo, we have chosen to measure the final PGE2 metabolites' content in the BAL fluid (PGEM, Cayman Chemical, Ann Arbor, MI). The PGEM levels were expressed as picograms per milliliter.

BAL fluid was also collected from animals receiving water for 14 days and then exposed to citric acid (0.1 M) aerosol for 10 min in order to investigate the acute effect of the irritant on these mediators.

BK concentration was measured by a competitive enzyme immunoassay kit (Peninsula Laboratories Inc, USA) following the manufacturer's protocol and expressed as nanogram per milliliter of BAL fluid.

### Drugs and chemicals

Zofenopril calcium was provided by Menarini A.M.M.L.S. (batch No: ZFNA442; Florence, Italy) and ramipril, by CHEMOS GmbH (batches No. 20070101 and 20081100; Regenstauf, Germany).

MEN16132 or 4-(S)-amino-5-(4-{4-[2,4-dichloro-3-(2,4-dimethyl-8-quinolyloxymethyl)phenylsulfonamido]-tetrahydro-2*H*-4-pyranylcarbonyl} piperazino)-5-oxopentyl](trimethyl)ammonium chloride hydrochloride was synthesized at the Chemistry Departments of Menarini Ricerche, Florence and Pomezia (Italy). Sodium pentobarbital and citric acid were purchased from Sigma-Aldrich.

### Statistical analysis

The total number of coughs detected in 10 min of citric acid aerosol exposition was expressed as the mean ± SEM of the given number of animals.

Statistical comparison among groups was performed by one-way analysis of variance followed by Student' s *t* test for unpaired data. The differences were considered significant at the level of $P<0.05$.

## Results

### General

No significant variation of the drinking solution volumes among groups (ACE inhibitors vs. controls) was observed throughout the experimental period. The daily adjusted doses of each ACE inhibitor, calculated after the previous day's water intake and body-weight check, didn't differ from the theoretical doses for the whole experiment.

### Citric acid-induced cough response

Inhalation of citric acid solution at increasing concentrations (0.1, 0.2, and 0.4 M) induced a dose-dependent cough response (13.0±2.5, 19.0±1.0, 25.0±0.9 number of coughs, respectively, $n$=4–7) during the 10 min of aerosol exposure (Fig. 1). The lower concentration (0.1 M) was chosen for further experiments to give reproducible and submaximal cough responses and to allow a better increase of the cough reflex after treatment with ACE inhibitors.

### Effect of ACE inhibitors' treatment on citric acid-induced cough

The effect of the 2-week oral treatment with zofenopril (10 mg/kg/day) or ramipril (3–10 mg/kg/day) in comparison to controls (water) was evaluated toward cough response induced by citric acid (0.1 M). Zofenopril did not change the

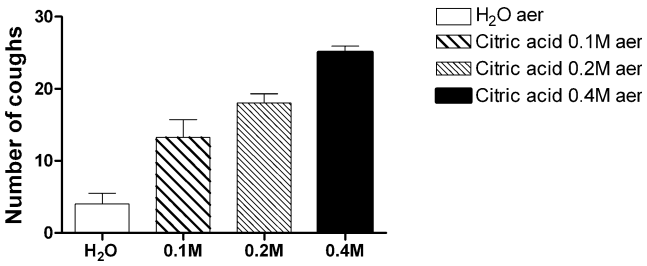


**Fig. 1** Effect of aerosol inhalation of increasing doses of citric acid (0.1–0.2–0.4 M) in comparison to the control group on the cough reflex. The number of coughs was measured during 10 min of aerosol exposition. Each value is the mean ± SEM of 4–7 experiments

number of coughs induced by citric acid (16.0±1.4, $n$=8) as compared to the control group (15.0±1.8, $n$=10; Fig. 2).

Ramipril caused a statistically significant increase, 40% (21.0±1.8) and 60% (24.0±2.5), in the number of coughs in comparison to the control group at the dose of 3 and 10 mg/kg, respectively.

### Effect of MEN16132 on ramipril-induced increase of cough caused by citric acid

The effect of the kinin $B_2$ receptor antagonist MEN16132 (0.25 mg/kg i.p.) was evaluated on cough induced by citric acid after daily oral administration of ramipril (10 mg/kg) for 14 days. MEN16132 significantly reduced the number of coughs measured during the exposure to citric acid after ramipril treatment by 26%, from 23±2 to 17±2 (Fig. 3). MEN16132 also significantly reduced the cough response caused by citric acid in control animals by 35%, from 17.0±2.0 to 11.0±2.0.

This data support the notion that bradykinin is involved in the citric acid-induced cough response, but they are not convincing to establish if bradykinin is really involved in the ramipril potentiation of cough. To investigate this point, we have measured bradykinin levels in the BAL fluid.

### Bradykinin and PGE2 levels in the BAL fluid

Bradykinin concentration measured in the BAL fluid, collected after 2 weeks of daily oral treatment with zofenopril (10 mg/kg), ramipril (10 mg/kg), or water (control group) increased significantly by 32% in the ramipril-treated group as compared to the control group (1.85±0.19 vs. 1.4±0.1 ng/ml, $n$=8–12; Fig. 4). On the contrary, BK levels in the BAL fluid of zofenopril-treated guinea pigs were not significantly different from controls and were significantly lower as compared to the ramipril-treated group.

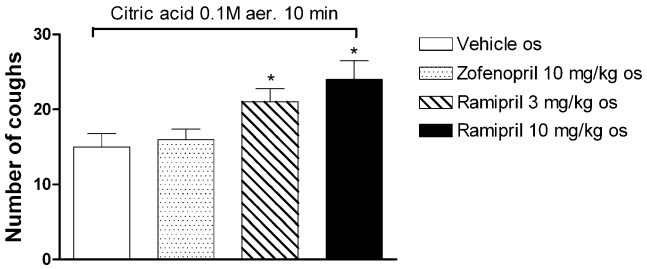


**Fig. 2** Effect of daily oral administration of zofenopril (10 mg/kg) and ramipril (3–10 mg/kg) for 14 days in drinking water on cough induced by the aerosol of 0.1 M citric acid solution performed at the end of the ACE inhibitors' treatment. The number of coughs was measured during the 10-min period of citric acid aerosol. Each value is the mean ± SEM of 8–10 experiments. *$P$<0.05 vs. vehicle- and zofenopril-treated group

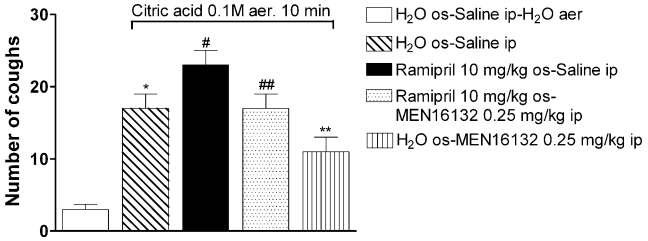


**Fig. 3** Effect of MEN16132 on cough induced by the aerosol of 0.1 M citric acid solution after daily administration of ramipril (10 mg/kg os in drinking water for 14 days) in guinea pigs. MEN16132 (0.25 mg/kg) was given intraperitoneally 30 min before citric acid aerosol performed at the end of ACE inhibitor treatment. Each value is the mean ± SEM of 7–12 experiments. *$P$<0.05 significantly different from control group, #$P$<0.05 significantly different from citric acid-induced cough, ##$P$<0.05 significantly different from ramipril-induced increase of cough, **$P$<0.05 significantly different from citric acid-induced cough

Aerosol of citric acid (0.1 M for 10 min), as a strong irritant stimulus, doubled the BK concentration in the BAL fluid of vehicle-treated guinea pigs (2.8±0.2 ng/ml, $n$=8).

PGE2 levels, measured as prostaglandin E2 metabolite (PGEM) in the BAL fluid of zofenopril-treated guinea pigs, were comparable with those found in the control group (22.0±2.0 pg/ml and 23.5±2.5 pg/ml, respectively; $n$=8–9; Fig. 5).

Ramipril increased significantly by 232% (78.0±13.0 pg/ml, $n$=4) in comparison with the control group, the amount of PGEM in the BAL fluid of guinea pigs.

For comparison, the exposure of vehicle control animals to citric acid aerosol (0.1 M for 10 min) increased PGEM levels by 353% (106.5±27.0 pg/ml, $n$=8) in the BAL fluid.

## Discussion

In this study, we have compared the effect of two ACE inhibitors, zofenopril and ramipril, at doses producing a comparable lowering of systolic blood pressure in SHR (Cushman et al. 1989a), on the citric acid-induced cough in

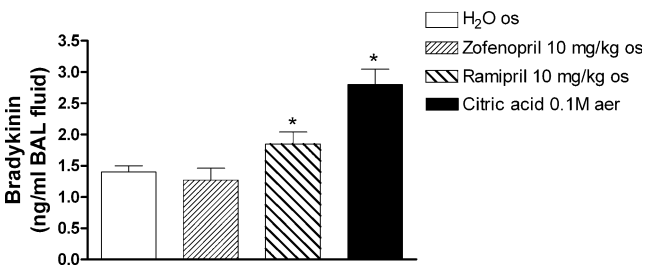


**Fig. 4** Bradykinin levels measured in the BAL fluid collected after 14 days of oral treatment with zofenopril (10 mg/kg/day) and ramipril (10 mg/kg/day) in comparison to the vehicle control group in guinea pigs. Bradykinin was also measured in BAL fluid collected 10 min after 0.1 M citric acid aerosol performed in the control group on the 14th day. Each value is the mean ± SEM of 8–12 experiments. *$P$<0.05 significantly different from the control and zofenopril-treated group

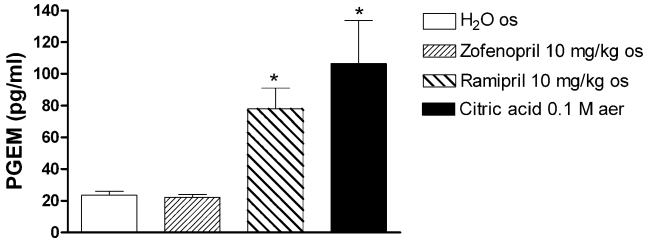


**Fig. 5** Determination of PGE2 levels, measured as PGE2 metabolites (*PGEM*), in the BAL fluid collected after 14 days of oral treatment with zofenopril (10 mg/kg/day), ramipril (10 mg/kg/day), or water (control group) in guinea pigs. PGEM was also measured in BAL fluid collected 10 min after 0.1 M citric acid aerosol performed in the control group on the 14th day. Each value is the mean ± SEM of 4–9 experiments. $^{*}P<0.05$ significantly different from the control and zofenopril-treated group

guinea pigs and the role of BK and PGE2 in mediating the potentiating response.

Our results have shown a differential activity of zofenopril and ramipril on cough; in fact, zofenopril did not increase the number of coughs induced by citric acid in the guinea pigs, while ramipril greatly and dose-dependently potentiated such response.

The difference between zofenopril and ramipril observed in inducing potentiation of cough provoked by citric acid might be related to various factors including the different pharmacokinetic profiles (Meisel et al. 1994; Marzo et al. 1999), the different tissue distributions, and also the different abilities of tissue and blood esterases to activate the two drugs. Both zofenopril and ramipril are prodrugs which need to be hydrolyzed in their active metabolites, zofenoprilat and ramiprilat respectively, by the esterases in blood and other tissues.

In this study, we have shown that the differences between zofenopril and ramipril on cough could be related to the different accumulations in the airways of mediators involved in cough production, such as BK and PGE2, which were measured after the repeated daily oral administration of the two ACE inhibitors for 2 weeks. Both BK and PGE2 have a role in the cough reflex. BK induces cough through the sensitization and direct stimulation of C-fiber nerve endings in the airways, via the $B_2$ receptor stimulation, (Fox et al. 1993; Fox et al. 1996) and also activates sensory C-fibers indirectly by inducing the local release of prostaglandins (Carr and Undem 2003). The stimulation of sensory nerve fibers by bradykinin and prostaglandins can in turn lead to the release of tachykinins, such as neurokinin A and substance P (Maggi 1993; Maggi et al. 1995) which may further induce cough by activating the tachykinin $NK_1$ and $NK_2$ receptors and sensitizing rapidly adapting receptors (Advenier et al. 1993; Joad et al. 1997).

We have shown that citric acid induces a marked release of BK and PGE2 in the airways. The increase of proton concentrations in the airways may stimulate, either directly or through bradykinin formation, capsaicin-sensitive sensory nerves which release tachykinins from their peripheral terminals causing bronchoconstriction and cough (Saria et al. 1988; Maggi 1993; Featherstone et al. 1996). Citric acid increases bradykinin levels in the airways through the release or activation of the enzyme kallikrein which, acting on kininogens, leads to bradykinin production (Featherstone et al. 1996). The increase of PGE2 levels in the airways caused by citric acid may be secondary to bradykinin formation which is known to increase PGE2 release through arachidonic acid release enhancement and cyclooxygenase stimulation (Pang and Knox 1997).

Evidence of BK involvement in cough caused by ACE inhibitors has been already shown in a previous study in which the increase of citric acid-induced cough in guinea pigs, observed after chronic treatment with captopril, was reduced by the kinin $B_2$ receptor antagonist Icatibant (Fox et al. 1996). Here, we have demonstrated that the enhancement of cough induced by ramipril was associated to the increase of BK in the BAL fluid and occurred through the activation of the bradykinin $B_2$ receptor since the potent and selective $B_2$ receptor antagonist MEN16132 (Cucchi et al. 2005; Valenti et al. 2005; Valenti et al. 2008) inhibited such response. On the contrary, BK levels were not increased in the BAL fluid of zofenopril-treated guinea pigs as compared to the control group.

In addition to the blockade of BK degradation, a peculiar nonenzymatic interaction of ACE inhibitors in terms of a cross talk between ACE, a transmembrane protein, and the seven-transmembrane $B_2$ receptor has been described in CHO cells expressing the human BK $B_2$ receptor and ACE (Minshall et al. 1997; Marcic et al. 1999). In fact, ACE inhibitors enhance BK binding, block receptor desensitization, and decrease receptor internalization, all effects contributing to potentiate BK effects. Likely, the lower incidence of cough seen in zofenopril compared to ramipril can be also ascribable to less interaction with the $B_2$ receptor. On the contrary, ramipril potentiation of cough could be greater because of the BK-binding enhancement and inhibition of receptor desensitization and internalization properties.

The role of inhaled PGE2 in cough production has been previously characterized in healthy volunteers (Costello et al. 1985) and in mouse and guinea pig where it induces the depolarization of sensory nerves through the activation of the EP3 receptor (Maher et al. 2009). Our results have demonstrated that PGE2 levels also markedly increased in the BAL fluid after repeated administration of ramipril, but they were not modified in zofenopril-treated animals. Interestingly, in a previous study, ramipril was shown to increase COX-2 expression in the lung of mice leading to an enhanced prostaglandin production which was inhibited by the selective COX-2 inhibitor celecoxib (Kohlstedt et al.

2005). Therefore, in addition to the increase of BK levels due to ACE inhibition, ramipril can induce a direct activation of PGE2 production via the increase of COX-2 expression. At further support of this evidence, the NSAIDs indomethacin and sulindac were shown to reduce cough in hypertensive patients treated chronically with captopril, indicating the involvement of prostaglandins in ACE inhibitor-induced cough (McEwan et al. 1990; Fogari et al. 1992).

Both zofenopril and ramipril are potentially able to increase BK levels in the airways, due to their specific mechanism of action as ACE inhibitors, although our data exclude this possibility for zofenopril at least at the doses tested. Higher dose of zofenopril (30 mg) was not tested due to the low solubility of the compound in water that did not allow us to perform the oral administration in the drinking water. In addition, currently, there is no evidence on the activation of prostanoid synthesis by zofenopril, suggesting that the key to explain the different effects of the two drugs on cough might be dependent on PGE2's increased production more than on the BK involvement. It has already been shown that captopril increased PGE2 synthesis in rat-isolated renal glomeruli and this effect was independent on bradykinin since it was unchanged in the presence of a kallikrein inhibitor (Galler et al. 1982).

In conclusion, the ACE inhibitor ramipril, orally administered for 2 weeks, produced a significant increase of cough provoked by citric acid in guinea pigs, possibly through mechanisms involving BK, through the $B_2$ receptor, and particularly, PGE2 production in the airways. On the contrary, zofenopril did not show any potentiation of citric acid-induced cough or BK and PGE2 increase in the airways. These favourable pharmacological characteristics of zofenopril can provide a more safe therapeutic application than other ACE inhibitors in humans.

**Conflict of interest** The authors declare that they have no conflict of interest.

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