Mechanism of Irritant-Induced Cough: Studies with a Kinin Antagonist and a Kallikrein Inhibitor

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Abstract. It has been suggested that bradykinin may play a role in stimulating cough in at least one pathological condition in humans. We have employed an animal model to investigate the possible role of this peptide in irritant-induced cough. The kinin antagonist Hoe 140 and codeine both produced dose-related inhibition of cough responses to inhalation of citric acid or bradykinin aerosols by conscious guinea pigs. The selective tissue kallikrein inhibitor CH694 inhibited cough caused by citric acid but not by bradykinin. Indomethacin pretreatment attenuated the responses to both stimuli as did phosphoramidon. It is concluded that cough produced by citric acid inhalation may be mediated, at least in part, by generation of kinins; secondary to this, a release of prostanoids also appears to participate in the response.

Key words: Cough—Bradykinin—Kallikrein

Introduction

Cough is a centrally coordinated reflex response to stimulation of peripheral cough receptors in the tracheobronchial tree [33]. As such, coughing is a protective reflex provoked by a variety of stimuli, including noxious gases or vapors, mechanical trauma, and viral infections of the upper respiratory tract. One possible link among these diverse provocants is the production of inflammatory mediators that may either directly activate or sensitize the cough receptors. There is some circumstantial evidence suggesting that the proinflammatory peptide bradykinin may play a role in mediating...
irritant-induced cough. Certainly, some patients treated with angiotensin-converting enzyme (ACE) inhibitors for cardiovascular disorders complain of persistent dry cough as a side effect [32]. An alteration of the sensitivity of the cough reflex to irritant stimuli as a result of decreased kinin metabolism due to ACE inhibition has been proposed as the mechanism underlying this phenomenon [18]. In both asthmatic and normal human subjects inhalation of bradykinin is reported to produce a sensation of retrosternal discomfort and cough [8], and ACE inhibitors have been shown to potentiate the bronchoconstrictor effects of bradykinin in an animal model [11]. The ability of bradykinin to stimulate sensory nerve endings in a variety of tissues including the airways is well known [10, 21, 26], as its ability to release prostaglandins [16, 31], themselves tussive agents [3]. Prostanoid release by kinins may account for the ability of the cyclooxygenase inhibitor sulindac to attenuate the cough response occurring in individuals treated with ACE inhibitors [17].

To elucidate further the role of bradykinin in mediating the cough response to noxious stimuli, the responses induced by exposure of conscious guinea pigs to aerosols of either bradykinin or citric acid were studied. Citric acid was chosen as the nonspecific noxious stimulus as it has been studied very extensively both in animal models [5, 7] and in human subjects [22, 25]. Indeed, inhalation of citric acid remains a commonly used investigational tool in human pulmonary pharmacology. For example, it has been used recently in studies on which specific nerve groups may be involved in cough in humans [27] and in studies on idiopathic cough in children [24]. The effects of a range of pharmacological manipulations on responses to the two stimuli were compared, including kinin antagonism employing the potent compound Hoe 140 [34]; inhibition of kallikrein, which cleaves lysyl bradykinin or bradykinin from high molecular weight precursors [9], by the novel tissue kallikrein-selective inhibitor CH694 [28, 29]; inhibition by phosphoramidon of neutralendopeptidase, the predominant kininase enzyme of the airways [14]; inhibition of cyclooxygenase with indomethacin; and central inhibition of the cough reflex with codeine.

Materials and Methods

Cough

Guinea pigs (male Dunkin Hartley strain, 450–600 g) were exposed to aerosols of citric acid or bradykinin solutions in 0.9% saline for periods of 3 min by placing them in a perspex chamber (4.3 liters) into which aerosols were generated from a Wright’s nebulizer driven by compressed air at 14 liters/min. The number of times that each animal coughed during this period was recorded by direct observation, the response being easily distinguished by a trained observer.

On the basis of preliminary experiments examining the dose-response curve for citric acid aerosols, a concentration of 1.4 M was chosen for routine provocation since this dose produced reproducible responses without effects lasting beyond the period of exposure. A typical response in one group of 10 animals was 15.2 coughs/3 min ± 2.5. Bradykinin was employed at a concentration of 9 mM. A typical response was 18.7 ± 2.3 coughs/3 min (n = 10).

Drug Effects on Cough

Examination of responses to repeated testing revealed that when animals were exposed to the same dose of citric acid on two to four occasions at intervals varying from 1 to 10 days after the initial exposure, no