Human responses to inhaled capsaicin are not inhibited by granisetron

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Cough is a common respiratory symptom, the mechanism of which is poorly understood. In this study the role of 5-HT₃ receptors was investigated. Capsaicin-induced cough and increase in airways resistance were measured in six male volunteers before and after infusion with granisetron 160 µg kg⁻¹ or placebo. Neither cough nor the increase in respiratory resistance was altered by the active treatment. These results suggest that 5-HT₃ receptors are not involved in these two respiratory responses to inhaled capsaicin in humans.

Keywords 5-HT cough reflex bronchoconstriction

Introduction

Cough is a common respiratory symptom (Fuller & Jackson, 1990) yet the mechanism by which the reflex is mediated in humans is uncertain (Karlsson *et al.*, 1988). The role of 5-HT as a modulator of the central relay of the cough reflex has been demonstrated in the cat. In the cat (Kamei *et al.*, 1986) increased levels of 5-HT in the CNS inhibit the cough reflex and 5-HT also acts as the final transmitter for opiate-induced suppression of cough (Yanaura *et al.*, 1981). So far, the subtype of 5-HT receptor mediating the modulatory effects of 5-HT on the cough reflex is not known. In the rat (Kilpatrick *et al.*, 1989) there is a high density of 5-HT₃ receptors in the area postrema of the midbrain, which would include the cough centre, and on the vagus nerve (Cunningham *et al.*, 1987). Moreover, 5-HT₃ receptors are present on the peripheral nerves (Richardson *et al.*, 1985) and such receptors on the vagus may be involved in vomiting (Andrews *et al.*, 1988). 5-HT has also been shown to sensitise the nerves arising in the lung which mediate reflex bronchoconstriction (Sheller *et al.*, 1982). Thus, 5-HT may have a role as modulator of both cough and reflex bronchoconstriction.

In humans, the role of 5-HT on respiratory reflex has been little studied. We have therefore investigated the role of 5-HT acting on 5-HT₃ receptors on respiratory reflexes in normal humans by assessing the effects of the specific 5-HT₃ antagonist granisetron (Fake *et al.*, 1987) on the cough reflex and reflex increase in airways resistance induced by inhaled capsaicin.

These data were presented at a meeting of the British Pharmacological Society in January 1990.

Methods

Six normal male volunteers aged 23–35 years took part in the study which had the approval of the Ethics Committee.

Challenges

Cough To induce cough the volunteers were asked to inhale single breaths of either saline or capsaicin 1.9–500 µM from a nebuliser controlled by a dosimeter. The doses were given in a random order and the number of coughs in the minute following the inhalation counted. Results were expressed as the concentration of capsaicin causing 2 (C2) or 5 (C5) or more coughs (Fuller *et al.*, 1988).

Respiratory resistance Respiratory resistance (Rrs) was measured using a forced oscillation technique (Fuller *et al.*, 1988). Three measurements of respiratory resistance were made before and after single breaths of capsaicin at doses which caused less than two coughs. The dose used was determined from the first cough response on each study day and the same dose was used throughout that study day.

Protocol Volunteers were studied on two occasions at least 1 week apart. A cannula was inserted into a forearm vein for infusion of granisetron. Baseline cough responses and Rrs measurements were made before and after capsaicin. Subjects then received an infusion of 160 µg kg⁻¹ of granisetron and placebo on separate dosing

Figure 1 Log concentration of capsaicin causing two or more coughs (C_2) (closed symbols) and concentration causing five or more coughs (C_5) (open symbols) before and after infusion of granisetron (triangles) $160 \mu\text{g kg}^{-1}$ or placebo (squares).

Figure 2 % increase in respiratory resistance following inhalation of a concentration of capsaicin that causes > two coughs before and after infusion of granisetron (triangles) $160 \mu\text{g kg}^{-1}$ or placebo (squares).

days, administered according to a randomised, double-blind, crossover protocol. Cough and respiratory responses were measured at 20, 90 and 180 min following treatment.

Statistics

The log concentration of capsaicin causing two or five or more coughs and the % change in respiratory resistance caused by capsaicin were analysed by multiple factor analysis of variance.

Results

The effect of treatment on C_2 and C_5 is shown in Figure 1 and on the % increase in Rrs in Figure 2. There were no statistically significant differences in either responses to capsaicin after either treatment compared with placebo.

Discussion

Capsaicin, when inhaled by normal volunteers, causes a reproducible cough (Collier & Fuller, 1985) and reflex

increase in airways resistance (Fuller *et al.*, 1985). The cough can be inhibited by topical local anaesthetics (Collier & Fuller, 1985; Choudry *et al.*, 1990) and systemic administration of opiates (Fuller *et al.*, 1988) and the increase in airways resistance by anticholinergic agents (Fuller *et al.*, 1985). Intravenous administration of a dose of granisetron, which would effectively inhibit vomiting caused by anti-cancer chemotherapy in humans (Carmichael *et al.*, 1989; Cassidy *et al.*, 1988) was without effect on either cough or reflex increase in airways resistance caused by inhaled capsaicin. This suggests that neither reflex in normal humans is under tonic influence of 5-HT acting through a 5-HT₃ receptor. Thus, if the human reflex is similar to that of the cat, then 5-HT is either only released under the influence of opiates, or it inhibits the reflex through a different sub-class receptor.

Further investigations are required by other agonists and antagonists which interact with 5-HT in order to elucidate the mechanism by which the cough reflex is transmitted in humans and thereby develop safer therapeutic options for cough than are currently available.

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