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# Modulation of capsaicin induced airway reflexes in humans: effect of monoamine oxidase inhibition

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1 In animal studies monoamine oxidase (MAO) inhibition has been shown to reduce the cough response through elevation of 5-HT in the central nervous system. In this study the effect of selective inhibition of the two subtypes of MAO (MAO-A and MAO-B) was studied on human airway reflexes.
2 Capsaicin-induced cough and reflex increase in respiratory resistance were measured in nine normal volunteers before and after MDL 72394 (MAO-A inhibitor) 16 mg or MDL 72974A (MAO-B inhibitor) 12 mg.
3 Neither inhibitor altered capsaicin-induced cough. Following treatment with MDL 72394, however, the capsaicin-induced reflex increase in resistance was enhanced, by 5.97 ± 2.1 fold of the placebo value at 1 h.
4 Thus, neurotransmitters in the central nervous system which are substrate for MAO-A (i.e. noradrenaline, 5-HT) may be involved in the control of capsaicin-induced reflex bronchoconstriction.

**Keywords** cough bronchoconstriction capsaicin monoamine oxidase inhibition

## Introduction

Both cough and reflex bronchoconstriction are important features of human respiratory disease. Although the sensory and efferent limbs of the reflexes are fairly well studied, the central relay mechanisms of both these reflexes in man are poorly understood. In the rat and cat both 5-hydroxytryptamine (5-HT) and noradrenaline acting at the $\alpha_2$-receptor, modulate cough and ventilatory reflexes (Igarashi *et al.*, 1990; Kamei *et al.*, 1986). In addition, 5-HT acts as the final neurotransmitter of opiate-induced suppression of cough in both the rat and cat (Ho & Takemori, 1989; Kamei *et al.*, 1988, Von-voigtlander *et al.*, 1984). In humans opiates, when given parenterally, also modulate both cough (Fuller *et al.*, 1988) and reflex bronchoconstriction (Sheppard *et al.*, 1984). The role of 5-HT in the relay of these airway reflexes needs to be investigated, although we have been unable to show any role for 5-$HT_3$ receptors in the sensitivity of the cough and bronchoconstrictor reflex in a previous study (Choudry *et al.*, 1991). In the cat, however, 5-hydroxytryptophan, the precursor of 5-HT, was shown to depress the cough reflex, an effect which was enhanced by non-selective inhibition of monoamine oxidase (MAO), the enzymes responsible for the catabolism of monoamine neurotransmitters (Kamei *et al.*, 1986).

In man, inhaled capsaicin causes both a dose-dependent cough (Collier & Fuller, 1984) and a transient increase in respiratory resistance (Fuller *et al.*, 1985). We have therefore investigated the effect of two selective MAO inhibitors, MDL 72394, an inhibitor of MAO type A (MAO-A) (Palfreyman *et al.*, 1985), and MDL 72974A, an inhibitor of MAO-B (Harland *et al.*, 1990; Zreika *et al.*, 1981) on the airway reflexes in humans stimulated by inhaled capsaicin. MAO-A and MAO-B differ in their anatomical distribution with MAO-A being more abundant than MAO-B in the periphery where inhibition of its action can have profound effects on sympathetic activity (Fowler & Ross, 1984). The two enzymes also differ in their metabolic profile (Denney & Denney, 1985; Fowler & Ross, 1984), however, the effect of inhibition of either enzyme will depend upon its relative amount and profile of neural transmitters within a potential site.

## Methods

Nine normal non-smoking male volunteers (aged 22 to 37 years) took part in this study which had the approval of the local hospital Ethics Committee.

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*Challenges*

*Cough* The volunteers inhaled single breaths of either vehicle or capsaicin 1.9–500 μM in 10% ethanol with 0.9% w/v saline from a nebuliser controlled by a dosimeter. The doses were given in a random order and the number of coughs occurring in the minute which followed each inhalation were counted (Fuller *et al.*, 1988). Results were expressed as the log dose of capsaicin causing three or more coughs ($D_3$).

*Respiratory resistance* Respiratory resistance (Rrs) was measured using a forced oscillation technique (Fuller *et al.*, 1988; Landser *et al.*, 1976). Three measurements of respiratory resistance were made before and a further measurement was made after single breaths of capsaicin at doses which caused less than two coughs. The dose used was determined from the first cough response challenge on each study day and the same dose was used throughout that study day.

*Analysis of data*

The log concentration of capsaicin causing three or more coughs and the per cent change in respiratory resistance caused by capsaicin were analysed by multiple factor analysis of variance for repeat measures.

*Protocol*

Volunteers attended on three occasions at least 3 weeks apart. The number of coughs caused by capsaicin, baseline respiratory resistance and the increase in respiratory resistance following inhalation of subtussive doses of capsaicin were recorded before and 1, 2 and 24 h after oral administration of capsules of either placebo, MDL 72394 16 mg or MDL 72974A 12 mg (Marion Merrell Dow, Strasbourg, France). The drugs were administered in a randomised double-blind manner. The doses used were the highest available for single dose administration to man and are doses which have been shown to be effective in man (Denny & Denny, 1985; Fowler & Ross, 1984; Harland *et al.*, 1990; Palfreyman *et al.*, 1985; Zreika *et al.*, 1989). Volunteers adhered to a standard low tyramine diet for 3 weeks following each drug administration.

## Results

*Cough*

Neither pretreatment with MDL 72394 nor MDL 72974A altered the concentration of capsaicin which caused three or more coughs (Figure 1). The power (1–β) of this study to detect one doubling dilution in this concentration was 99%.

*Respiratory resistance*

Baseline Rrs measured did not differ on the 3 study days (Table 1). In addition, there were no significant changes in Rrs measured before capsaicin challenge over each 24 h observation period (Table 1). Figure 2 illustrates that the mean (95% CI) pretreatment increases in Rrs caused by a single inhalation of capsaicin was similar on all 3 days, being 20.2 ± 8.8%, 20.5 ± 8.1% and 14.4 ± 4.8% on the 3 study days. Following placebo, there was a reduction in the responses of Rrs to inhaled capsaicin to 9.7 ± 9.2% at 1 h. The capsaicin-induced increase in Rrs was enhanced significantly compared with pretreatment and placebo to 32.1 ± 22.8% at 1 and 28.6 ± 1.98% at 2 h after treatment with MDL 72394 ($P < 0.05$) but the

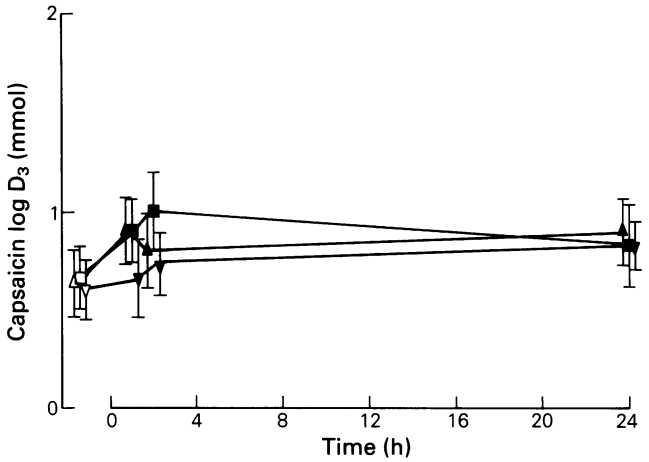


**Figure 1** The log dose of capsaicin which caused three or more coughs before (open symbols) and 1, 2 and 24 h after treatment with MDL 72974A (12 mg, ▼), MDL 72394 (16 mg ▲) or placebo (■) ($n = 9$).

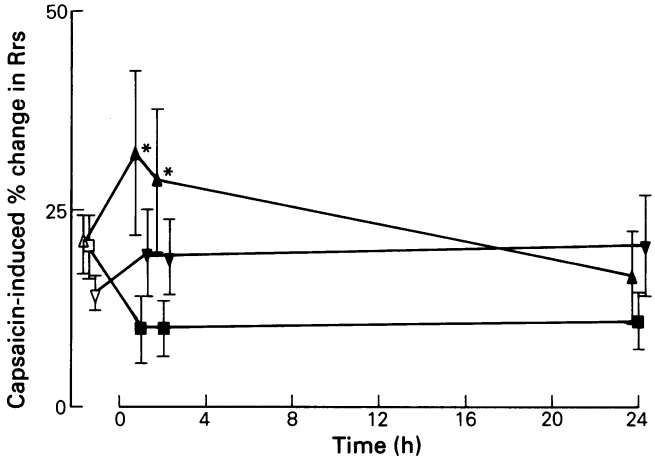


**Figure 2** The mean ± s.e. mean % increase in Rrs caused by the inhalation of a subtussive dose of capsaicin before (open symbols) and 1, 2 and 24 h after treatment with MDL 72974A (12 mg, ▼), MDL 72394 (16 mg, ▲) or placebo (■) ($n = 9$). * = $P < 0.05$ compared with placebo.

**Table 1** Mean ± s.e. mean baseline Rrs (cm water $l^{-1}$ $s^{-1}$) before (pre) and at 1, 2 and 24 h after treatment with placebo, MDL 72974A 12 mg and MDL 72394 16 mg, $n = 9$

| | *Placebo* | *MDL 72974A* | *MDL 72394* |
|---|---|---|---|
| Pre | 2.44 ± 0.19 | 2.64 ± 0.24 | 2.58 ± 0.28 |
| 1 h | 2.36 ± 0.19 | 2.50 ± 0.22 | 2.44 ± 0.22 |
| 2 h | 2.41 ± 0.20 | 2.49 ± 0.20 | 2.43 ± 0.22 |
| 24 h | 2.40 ± 0.22 | 2.48 ± 0.24 | 2.26 ± 0.24 |

difference was no longer significant at 24 h. The potentiation at 1 h was 5.97 ± 2.11 fold following MDL 72 94 as compared with placebo. MDL 72974A caused no significant change in the capsaicin-induced change in Rrs compared with placebo the increase being 19.4 ± 12.1% at 1 h. These changes following MDL 72974A compared with placebo was not significant in absolute terms or when compared as change from the pre-treatment value. The results after MDL 72394 and MDL 7297A were not significantly different.

## Discussion

The results of the present study indicate that drugs which selectively inhibit the activity of MAO-A (Palfreyman *et al.*, 1985) and MAO-B (Harland *et al.*, 1990; Zreika *et al.*, 1989) both in the peripheral and central nervous system, have no effect on the cough reflex to capsaicin in normal volunteers. This suggests that neurotransmitters which are substrates for these enzymes are not involved in the regulation of the normal tone of the cough reflex unless there is a balance between two transmitters with opposing effects both of which are metabolised by MAO. This does not, of course, rule out a role for 5-HT in the abnormal sensitivity to the cough reflex seen in patients with cough (Fuller & Jackson, 1990) or that 5-HT may be the final transmitter in the opiate-dependent inhibition of cough in humans (Ho & Takemori, 1989; Kamei *et al.*, 1988; Kamei *et al.*, 1990; Vonvoigtlander *et al.*, 1984).

Interestingly, however, the two inhibitors had different effects on the reflex induced increase in Rrs following capsaicin inhalation (Fuller *et al.*, 1985). Despite having no effect on baseline tone, the MAO-A inhibitor MDL 72394 caused a marked potentiation of the reflex increase in Rrs at 1 and 2 h. The MAO-B inhibitor, MDL 72974A, did not, on the other hand, significantly modify this response compared with placebo.

Inhibition of MAO-A will preferentially modify the metabolism of 5-HT and noradrenaline, increasing the concentrations of these monoamine, whereas MAO-B inhibition will increase the concentrations of substrate for MAO-B, i.e. dopamine and β-phenylethylamine (Denney & Denney, 1985; Fowler & Ross, 1984). The net effect on the concentrations of each neurotransmitter will depend, however, on the relative amount of MAO-A and B and the degree of inhibition achieved at the site of action. It is unlikely that 5-HT, noradrenaline and dopamine are exerting an effect on the reflex respiratory responses examined in the present study in the peripheral nervous system, as any potentiation of the sensory limb of the reflex should cause an increase in cough (Christian *et al.*, 1989). Thus, it would be expected that both drugs should increase capsaicin-induced cough which clearly was not the case. Moreover, since adrenergic nerves do not supply airway smooth muscle (Ind & Barnes, 1988) modulation of monoamine neurotransmitter concentrations at this site would not be expected to have a significant effect. There is thought to be sympathetic supply to the ganglia, however, increased activity at this site would be inhibitory rather than causing potentiation (Ind & Barnes, 1988).

It is possible that 5-HT, if increased locally, could potentiate the bronchoconstrictor effect of released acetylcholone (Sheller *et al.*, 1982). If this was the case, however, it would seem unlikely that 5-HT would be acting through stimulation of $5\text{-HT}_3$ receptors which are found on the vagal nerves (Kilpatrick *et al.*, 1989), since the selective $5\text{-HT}_3$ receptor antagonist granisetron was without effect in similar human studies (Choudry *et al.*, 1991). The effect of 5-HT in the central nervous system will of course vary depending on the site of delivery and the sub-type of receptor stimulated by the agonist used. However, 5-HT acting through the $5\text{-HT}_{1a}$ receptor in the rat (Igarashi *et al.*, 1990) causes suppression of cough.

The most likely explanation of the findings of the present study is that the central transmitter for the bronchoconstriction is noradrenaline. Following stimulation of the airway sensory nerves there would be a transient increase in the concentration of noradrenaline in the relay. Following treatment with the MAO-A inhibitor its concentration will be increased to a greater extent following inhibition of MAO-A than following inhibition of MAO-B. Noradrenaline is a good candidate as noradrenaline in the central nervous system acting on $\alpha_2$-receptors stimulates ventilation (Bolme *et al.*, 1974) and in man the centrally acting $\alpha_2$-receptor agonist clonidine has been shown to cause potentiation of histamine-induced bronchoconstriction to a greater extent than the peripherally acting $\alpha_1$-receptor agonist rilmenidine (Dinh Xuan *et al.*, 1988). This effect could be explained by an increased reflex component of the histamine response and requires further investigation. The results for the MAO-B inhibitor were intermediate between and not different from those of placebo and the MAO-A inhibitor. This could reflect either a lack of power of the study to resolve a difference or a partial effect of the drug within the relay on noradrenaline.

These results suggest that the transmitter of capsaicin-induced reflex bronchoconstriction in the central nervous system may be a substrate for MAO-A and thus could be noradrenaline. Further investigation is required to clarify the role of noradrenaline in this reflex. This is not only of interest with regard to the physiology of the system but may unmask new therapeutic targets for the treatment of human respiratory disease.

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