

Adaptation of cough reflex with different types of stimulation

To the Editor:

The recent paper in this journal by MORICE *et al.* [1] lends considerable insight into the different mechanisms of adaptation of the cough response to citric acid (CA), nebulised distilled water (NDW) and capsaicin. The relative absence of tachyphylaxis with continuous tidal breathing of capsaicin over 1 minute tends to corroborate previous reports that capsaicin is predominantly a stimulant of unmyelinated C-fibres which adapt slowly, while NDW and CA stimulate rapidly-adapting myelinated fibres.

The observation that significant tachyphylaxis occurs with repeated inhalation of capsaicin at 10 minute intervals for 40 minutes is consistent with data which we have recently collected in 18 subjects. We constructed concentration-response curves by administering single breaths ($0.008 \text{ mls} \cdot \text{breath}^{-1}$) of doubling concentrations of capsaicin from 0.5 – $500 \mu\text{M}$ at 1 minute intervals from a breath-activated nebulizer/dosimeter. The number of coughs in the 1 minute period following each breath was recorded and the challenge stopped when the lowest concentration which elicited 5 or more coughs (C5) had been administered. Fifteen minutes later we administered 2 breaths of C5 (30 seconds apart) at 0, 1, 3, 5, 10, 20, 30 and 60 minutes. The number of coughs in response to either of the 2 breaths at 0 minutes (baseline) was not significantly different to the response to C5 from the initial concentration-response challenge (mean \pm SEM coughs in response to 2 breaths at baseline = 9.9 ± 0.26). The cough response at 1 minute (9.1 ± 0.54) was similar to the baseline response which is consistent with the observation of Morice *et al.* that minimal tachyphylaxis occurs over this period. The response at all subsequent time points was significantly less than baseline however ($p<0.001$), reaching its lowest at 5 minutes (7.6 ± 0.38). The response had almost recovered at 60 minutes (8.5 ± 0.41). These data confirm the observation of Morice *et al.* that tachyphylaxis of the cough response to capsaicin occurs with repeated inhalation over 40 minutes.

However, we have also performed capsaicin challenges (to construct concentration-response curves as outlined above) at 0 (baseline), 1 and 2 hours in 16 subjects and at 0, 1 and 4 hours in 23 subjects and in these studies there was no significant difference in log C5 (or log C2, the lowest concentration which elicits 2 or more coughs) between the baseline and subsequent challenges (table 1). Significant tachyphylaxis therefore does not occur when capsaicin

challenge is repeated at intervals of 1 and 3 hours. This is at variance with the data of Morice *et al.* although the methods used in the two studies were different. In addition we have performed capsaicin challenges as outlined above at an average interval of 7 days (5–10 days) at the same time on each day in 40 subjects. There was no significant difference between the two challenges for either log C2 or log C5. The difference between the two challenges (number of doubling dilutions) for C2 and C5 were 0.85 ± 0.15 and 0.93 ± 0.16 respectively, indicating that the results of challenge were highly repeatable. In the study of Morice *et al.* capsaicin challenge was also highly repeatable at 1 week.

No. of subjects	Time	Log C2	Log C5
16	Baseline	0.93 ± 0.12	1.67 ± 0.17
	1 hour	1.08 ± 0.15	1.83 ± 0.17
	2 hours	1.07 ± 0.16	1.66 ± 0.20
23	Baseline	0.91 ± 0.07	1.89 ± 0.14
	1 hour	1.05 ± 0.10	2.02 ± 0.13
	4 hours	1.04 ± 0.08	2.06 ± 0.14

Figures are mean \pm SEM log concentration capsaicin (M).

Interpretation of results of studies in which relatively high doses of capsaicin are repeatedly administered at 3–30 minute intervals must take account of tachyphylaxis which occurs over this period. Significant tachyphylaxis does not occur, however, with repeated capsaicin challenge at intervals of 1 and 3 hours or repeated challenges at the same time on different days. The capsaicin model is therefore suitable for studies on the pharmacology of cough in man, especially where a shift in the concentration-response relationship is sought at intervals of an hour or more.

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Reference

1. Morice AH, Higgins KS, Yeo WW. – Adaptation of cough reflex with different types of stimulation. *Eur Respir J*, 1992; 5: 841–847.

Reply from the authors:

In their comment on our report [1] Drs O'Connell, Thomas and Pride provide us with additional data in general supporting our findings of significant tachyphylaxis with repeated cough challenge. Their studies in contrast to ours deal only with capsaicin induced cough but the degree of similarity in studies of acute tachyphylaxis is striking.

Where an apparent difference in our data exists is in the long-term tachyphylaxis studies: we found that capsaicin induced cough was significantly attenuated at 360 minutes after initial cough challenge, whereas O'Connell and co-workers found no tachyphylaxis at 60 and 240 minutes. We believe that methodological differences between the two studies explain this apparent contradiction. We performed repeated, intense cough challenges at 10 minute intervals for 40 minutes before the observation period of 360 minutes. In contrast O'Connell performed a single concentration-response challenge with a subsequent observation period of 60 and 240 minutes. Thus our experimental protocol produced a much more intense stimulation of the cough reflex and was more likely to detect long-term tachyphylaxis, should it be present.

Since it appears that only very intense stimulation of the cough reflex by capsaicin leads to down-

regulation of the cough response, several possibilities exist to explain this phenomenon. As suggested in our original article, inhibitory efferent nerves may depress afferent sensory traffic. However, intense capsaicin stimulation has also been shown to deplete sensory neurotransmitters within afferent nerves [2]; it is interesting to note that a similarly intense stimulation of the cough reflex produced much less subsequent inhibition when we used citric acid as the tussive agent. Alternatively, a dose-dependent desensitisation of neuronal responses has been described with capsaicin administration which appears to be the first manifestation of the long-term neurotoxic action of this agent [2].

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References

1. Morice AH, Higgins KS, Yeo WW. - Adaptation of the cough reflex with different types of stimulation. *Eur Respir J*, 1992; 5: 841-847.
2. Holzer P. - Capsaicin: cellular targets, mechanism of action and selectivity for thin sensory neurones. *Pharmacol Rev*, 1991; 43(2): 143-201.