2 Reinheimer, T. *et al*. (1995) *Am. J. Physiol*. 270, L722–L728
3 Klapproth, H. *et al*. (1997) *Naunyn-Schmiedeberg's Arch. Pharmacol*. 355, 515–523
4 Wessler, I., Kirkpatrick, C. J. and Racké, K. (1998) *Pharmacol. Ther*. 77, 59–79
5 Reinheimer, T. *et al*. (1998) *Eur. J. Pharmacol*. 349, 277–284
6 Grando, S. A. (1997) *J. Invest. Dermatol. Symp. Proc*. 2, 41–48
7 Sastry, B. V. R. and Sadavongvivad, C. (1979) *Pharmacol. Rev*. 30, 65–132
8 Klapproth, H., Racké, K. and Wessler, I. (1994) *Naunyn-Schmiedeberg's Arch. Pharmacol*. 349 (Suppl.), R72
9 Klapproth, H., Racké, K. and Wessler, I. (1998) *Naunyn-Schmiedeberg's Arch. Pharmacol*. 357, 472–475
10 Reinheimer, T., Baumgärtner, D., Höhle, K-D., Racké, K. and Wessler, I. (1997) *Am. J. Resp. Crit. Care Med*. 156, 389–395
11 Wessler, I., Hellwig, D. and Racké, K. (1990) *Naunyn-Schmiedeberg's Arch. Pharmacol*. 342, 387–393
12 Racké, K., Bähring, A., Brunn, G., Elsner, M. and Wessler, I. (1991) *Br. J. Pharmacol*. 103, 1213–1217
13 Racké, K. *et al*. (1992) *Am. Rev. Resp. Dis*. 146, 1182–1186
14 Starke, K., Göthert, M. and Kilbinger, H. (1989) *Physiol. Rev*. 69, 864–989
15 Fuder, H. and Muscholl, E. (1995) *Rev. Physiol. Biochem. Pharmacol*. 126, 265–412
16 Brunn, G., Wessler, I. and Racké, K. (1995) *Br. J. Pharmacol*. 116, 191–198
17 Racké, K., Brunn, G., Elsner, M. and Wessler, I. (1993) *Naunyn-Schmiedeberg's Arch. Pharmacol*. 348, 21–27
18 Wessler, I. *et al*. (1994) *Br. J. Pharmacol*. 113, 1221–1230

Folkerts and Nijkamp reply

Airway epithelium: more than just a source for epithelium-derived relaxing factors!

We thank Ignaz Wessler, Charles Kirkpatrick and Kurt Racké for their interest in our review[1]. We apologize for not including the references of these authors when mentioning that acetylcholine can be released by the epithelium and that the epithelium contains the synthesizing enzyme choline acetyltransferease[2–5]. However, as pointed out in the abstract, our aim was to focus on the pharmacological relevance of the putative epithelium-derived relaxing factors prostaglandin E_2 and NO in the modulation of airway tone. Further, special attention was paid to the role of both epithelium-derived relaxing factors in the development of airway hyperresponsiveness in animal models and in patients with asthma.

Acetylcholine, although released by the epithelium, is a contractile factor – if it modulates airway function in a positive way, it does so by an indirect action[5]. By contrast, our review highlighted the direct actions of prostaglandin E_2 and NO on smooth muscle[1]. This was also the reason why the action of epithelium-derived relaxing factors on the release of autonomic neurotransmitters (neuro-epithelium interaction) was not discussed. Moreover, we were limited in the amount of text and the number of references that we could include. Nevertheless, the timely finding that epithelium can synthesize and release acetylcholine was so interesting that we presented it as a fact together with the ability of the epithelium to release mucus, cytokines, and chemokines as well as the ability of the epithelium to metabolize histamine and neuropeptides (all without references).

For clarity, it should be pointed out that acetylcholine is probably not the only neurotransmitter, nor is it the only contractile mediator, released by the epithelium. In rat trachea, removal of the epithelium reduced the tissue content of noradrenaline by about 30%. Moreover, the overflow of noradrenaline evoked by electrical stimulation of epithelium-denuded tracheas was reduced by 70–80%, which suggests that the epithelium was involved in the release of noradrenaline[6]. It is well recognized that arachidonic acid can be metabolized by airway epithelial cells[7,8] and that these products can influence airway tone and reactivity[9]. Recent evidence showed that the inherent tone of the human bronchus was maintained by a balance between 5-lipoxygenase and cyclooxygenase products formed by the epithelium[10]. Vasopressin and substance P immunoreactivity in cultured and intact epithelium from rabbit tracheae has also been demonstrated[11]. In addition, endothelin can be produced by human and animal airway epithelial cells[12,13].

A number of investigations have pointed to a role for endothelin in modulating airway responsiveness and asthmatic reactions[14–16]. As described in the review, endothelin induces a potent contraction in epithelium-denuded tissues. However, it appears that a number of agents that have a contractile action on smooth muscle cause a relaxation when applied to the mucosal side of the airways[1]. Indeed, endothelin induces a NO-dependent relaxation of tracheae that contain epithelium[17]. In a recent study, airway hyperresponsiveness to methacholine was observed in endothelin knock out-mice[18]. Interestingly, NO-synthesis inhibition in endothelin 1 (+/+) wild-type mice significantly enhanced methacholine responsiveness, whereas this pretreatment did not modulate airway responsiveness in endothelin knockout mice[18]. These results support the hypothesis presented in our review that, in asthmatic patients, the airway hyperresponsiveness to a variety of contractile agents might be explained by a diminished production of epithelium-derived relaxing factors[1].

Finally, it should be concluded that the airway epithelium is more than just a source of epithelium-derived relaxing factors!

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References

1 Folkerts, G. and Nijkamp, F. P. (1998) *Trends Pharmacol. Sci*. 19, 334–341
2 Reinheimer, T. *et al*. (1996) *Am. J. Physiol*. 270, L722–L728

3 Klapproth, H. *et al.* (1997) *Naunyn-Schmiedebergs's Arch. Pharmacol.* 355, 1–9
4 Reinheimer, T., Munch, M., Racké, K., Kirkpatrick, C. J. and Wessler, I. (1998) *Eur. J. Pharmacol.* 349, 277–284
5 Wessler, I., Kirkpatrick, C. J. and Racké, K. (1998) *Pharmacol. Ther.* 77, 59–79
6 Racké, K., Bähring, A., Brunn, G., Elsner, M. and Wessler, I. (1991) *Br. J. Pharmacol.* 103, 1213–1217
7 Holtzman, M. J. (1992) *Annu. Rev. Physiol.* 54, 303–329
8 Holtzman, M. J., Zhang, V., Hussain, H., Roswit, W. T. and Wilson, J. D. (1994) *Ann. New York Acad. Sci.* 744, 58–77
9 Raeburn, D. (1990) *Gen. Pharmacol.* 21, 11–16
10 Watson, N., Magnussen, H. and Rabe, K. F. (1997) *Br. J. Pharmacol.* 121, 1099–1104
11 Rennick, R. E., Loesch, A. and Burnstock, G. (1992) *Thorax* 47, 1044–1049
12 Shima, H. *et al.* (1995) *Biochem. Mol. Biol. Int.* 37, 1001–1010
13 Mullol, J. *et al.* (1996) *Neuropeptides* 30, 551–556
14 Redington, A. E. *et al.* (1995) *Am. J. Resp. Crit. Care Med.* 151, 1034–1039
15 Chalmers, G. W., Little, S. A., Patel, K. R. and Thomson, N. C. (1997) *Am. J. Resp. Crit. Care Med.* 156, 382–388
16 Hay, D. W., Henry, P. J. and Goldie, R. G. (1993) *Trends Pharmacol. Sci.* 14, 29–32
17 Filep, J. G., Battistini, B. and Sirois, P. (1993) *Br. J. Pharmacol.* 109, 637–644
18 Nagase, T. *et al.* (1998) *Am. J. Resp. Crit. Care Med.* 157, 560–564

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