tor.

NO has been reported to inhibit mast cell reactivity; in contrast, the superoxide anion contributed to mast cells activation,[19] while MB is capable of generating superoxide[11-13] and inhibiting NO synthesis.[14] These reports imply the possibility that MB-induced tracheal contraction may be due to histamine release from mast cell degranulation. Therefore, by using compound 48/80 (a mast cell activator) (2 mg/ml) and sodium cromolyn (a mast cell stabilizer) (100 μM), we tested the relation between tracheal mast cells and MB-induced tracheal contraction. Our results (Fig. 3) indicate that tracheal mast cells do not seem to be involved in MB-induced contraction.

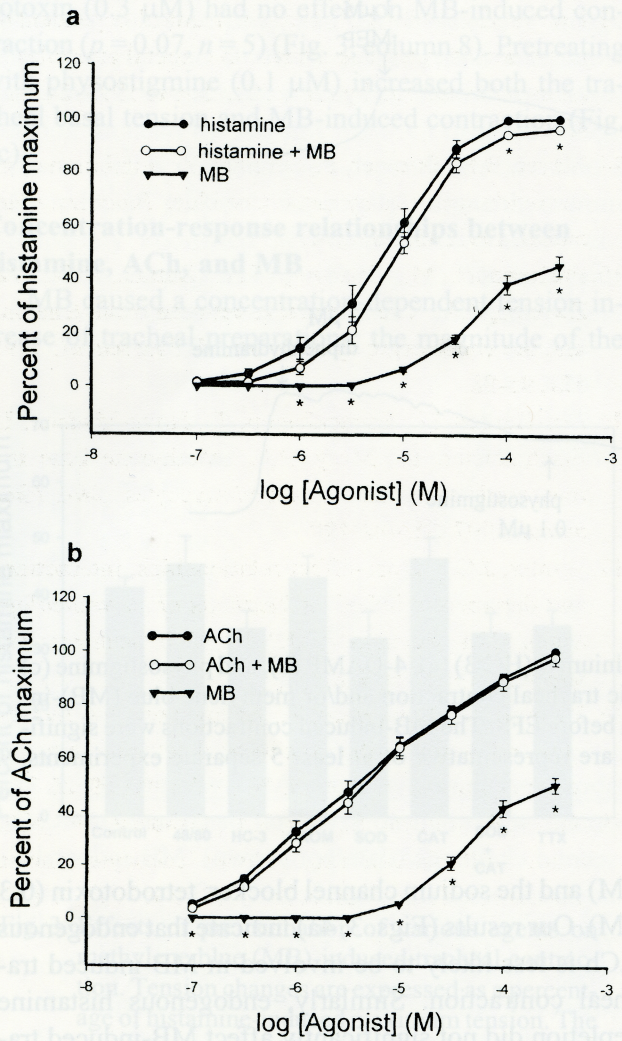

Fig. 5. Cumulative concentration-response curves for tension increases of guinea pig tracheal preparations caused by histamine and methylene blue (a), and ACh and methylene blue (b). Each point represents the mean ± S.E.M. of 5 experiments. Indomethacin (3 μM) was present throughout. * $p < 0.05$ as compared with the histamine (a) or ACh (b) value.

The above findings, coupled with the observation that the combined effects of full agonists and MB on tracheal tension were less than those of full agonists alone (Fig. 5a), led us to propose that MB may be a partial agonist of histamine receptors. However, the possibility that MB is also a partial agonist of ACh receptors can not be excluded based on the fact that ACh receptor antagonists attenuate MB-induced contraction (Fig. 2). In concert with this observation, MB has been reported to be a muscarinic antagonist in cardiac myocytes.[16]

In conclusion, we propose that inhibition of prostaglandin synthesis is responsible for the relaxation phase induced by MB alone. Diphenhydramine completely but 4-DAMP, atropine, and mepyramine partially attenuated MB-induced tracheal contraction. Meanwhile, depletion of endogenous ACh and histamine did not significantly affect MB-induced tracheal contraction. These findings imply that MB-induced tracheal contraction may be accompanied by the nonselective binding of ACh and histamine receptors.

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REFERENCES

1. Moncada, S., Palmer, R.M., Higgs, E.A. Nitric oxide: physiology, pathophysiology and pharmacology. *Pharmacol. Rev.* 1991, **43**, 109-142.
2. Gaston, B., Drazen, J.M., Jansen, A., Sugarbaker, D.A., Loscalzo, J., Richards, W., Stamler, J.S. Relaxation of human bronchial smooth muscle by S-nitrosothiols in vivo. *J. Pharmacol. Exp. Ther.* 1994, **268**, 978-984.
3. Jones, K.A., Lorenz, R.R., Warner, D.O., Katusic, Z.S.,