HYPERRESPONSIVENESS IN GUINEA-PIG ISOLATED RESPIRATORY PREPARATIONS FOLLOWING INHALATION OF OZONE

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Airway hyperresponsiveness can be defined as an increase in sensitivity to a wide variety of airway narrowing stimuli (Sterk & Bel 1989). In vivo, the hyperresponsive state has been induced by various agents including sensitisation with antigen (Daffonchio et al 1988), or exposure to PAF (Fitzgerald et al 1987) or ozone (Yeadon et al 1990). However, there are few reports of in vitro hyperresponsiveness. Holroyde & Norris (1988) showed a small, but insignificant, increase in tracheal responsiveness after exposure to ozone.

This study investigates the effects of ozone inhalation on the responses to various bronchoconstrictor agents in guinea-pig isolated trachea and perfused lungs.

Male Dunkin-Harley guinea-pigs (450-550g) were exposed to ozone (1.2ppm), in an exposure box, for 2½ h; control animals breathed laboratory air in the same box. The animals were then killed and isolated tracheal spirals (3-4cm, resting tension 1g) immersed in Krebs-bicarbonate solution (37.5°C) gassed with 5% CO_2 in oxygen. After 60 min equilibration, cumulative concentration-response curves to carbachol, histamine and potassium chloride (KCl) were constructed.

The lungs were perfused via the tracheal stump with warmed and gassed Krebs-bicarbonate solution at 5 ml min^{-1} and perfusion pressure recorded. Bolus injections were given in the order carbachol (10µg), histamine (30µg), adenosine (300µg) and KCl (100mg).

In tracheae from ozone-treated animals, carbachol induced contractions significantly greater than in control tissues at all concentrations. The maximum responses were 1.94±0.14g (n=5) in ozone treated and 1.29±09.13g in controls (n=4). When expressed as a percentage of the maximum responses, however, there was only a small insignificant increase in sensitivity after ozone (EC50 0.12(0.06-0.22µM in controls; 0.062(0.034-0.11)µM after ozone). In contrast, histamine showed no increase in either magnitude of response or in sensitivity (EC50 0.69(0.33-1.44)µM in controls; 1.77(0.34-9.22)µM after ozone). The maximum response to KCl was greater after ozone treatment (0.83±0.1g) than controls (0.65±0.09g) but not significantly. Furthermore, responses at lower concentrations and the EC50 values (2.12(0.51-8.94)mM in controls, 6.71(3.79-11.8)mM after ozone) showed no significant increase in responsiveness.

In the perfused lung, again it was only carbachol that showed a significant increase in response (32.1±6.3mm Hg in ozone-treated, 11.4±1.1mm Hg in controls). Constrictor responses to histamine (49.0±8.3 and 55.3±8.2mm Hg), adenosine (1.8±1.8mm Hg and 2.3±0.9mm Hg) and KCl (40.8±12.7 and 48.7±6.3mm Hg) did not differ significantly between controls and ozone treated respectively.

In conclusion, hyperresponsiveness of isolated tracheae and lungs was observed after ozone inhalation (1.2ppm for 2½h), but this was only apparent for carbachol-induced constriction, as an increase in response magnitude. Whether this represents a specific effect upon contractions mediated via muscarinic receptors remains to be established.

Sterk, P.J., Bel, E.M. (1989) Eur. Resp. J. 2 : 267-274
Fitzgerald, M.J. et al (1987) Br. J. Pharmacol. 90 : 112P
Yeadon, M. et al (1990) Ibid. 99 : 191P
Daffonchio, L. et al (1988) Ibid. 94 : 663-668
Holroyde, M.C. & Norris, A.A. (1988) Ibid. 94 : 938-946