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THE ACTION OF SODIUM CROMOGLYCATE ON 'C' FIBRE ENDINGS IN THE DOG LUNG

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The effect has been studied of sodium cromoglycate (SCG) on the activity of 'C' fibre sensory nerve endings in the canine lung. Pretreatment with SCG (100 μg/kg i.v.) reduced the excitation of these endings by capsaicin (10 μg/kg i.v.) for approximately 45 min. This property of SCG may explain its ability to suppress certain types of bronchoconstrictor responses in man.

Introduction Sodium cromoglycate (SCG) is a drug frequently used in the prophylactic treatment of bronchial asthma. Although the alleged mode of action of this drug is by stabilization of the mast cell (Cox, 1976), it can in some patients, inhibit bronchoconstrictor responses induced by methacholine and histamine in which mast cell disruption is not obviously involved (Woenne, Kattan & Levison, 1979). Since the drug is neither atropine-like, nor an antihistamine and it does not relax bronchial smooth muscle (Cox, 1976) its mode of action in these cases is obscure. One possible explanation is that it affects sensory nerves which can influence airway calibre, and so interfere with the reflex component of these bronchoconstrictor responses.

Russel & Lai-Fook (1980) have shown that stimulation of 'C' fibre sensory nerve endings in the dog lung with capsaicin can initiate reflex bronchoconstriction. By recording discharges in afferent 'C' fibres arising in the lungs of anaesthetized dogs we have shown that SCG can suppress the excitation induced by capsaicin.

Methods Beagle dogs were anaesthetized with chloralose (80 mg/kg i.v. followed by 10 to 15 mg/kg every 15 min) after induction with thiopentone sodium (10 mg/kg i.v.). The dogs were intubated and, after skeletal muscle paralysis (succinylcholine 1.5 mg/kg every 15 min), artificially respired. The chest was opened along the mid-line and the vagi were cut at the level of the diaphragm. The cervical vagosympathetic nerves were divided and impulses were recorded, using conventional electrophysiological equipment (Dixon, Jackson & Richards 1979), from fine strands (containing one or two actual fibres) teased from the distal end of the left cervical vagus. Lung 'C' fibre endings were identified by their sparse and irregular pattern of discharge, by their response to hyperinflation (3 to 4 tidal volumes) and capsaicin (10 μg/kg i.v.), and some by the conduction velocities of their fibres. Conduction velocity was measured according to the method of Coleridge & Coleridge (1977). Finally all endings used in the study were located in the lung by mechanical stimulation.

In each experiment total lung resistance (R_L) and dynamic lung compliance (C_{dyn}) were measured continuously according to the method of Amdur & Mead (1958). Details of these measurements have been described previously (Dixon *et al.*, 1979).

Body temperature, end tidal CO_2 and arterial blood Po_2, Pco_2 and pH were continuously monitored and kept within normal limits.

When a suitable fibre had been selected its response to capsaicin (10 μg/kg i.v.) was measured before and 10 min after SCG (100 μg/kg i.v.). In some cases several responses to capsaicin were obtained post SCG.

Capsaicin was dissolved as described by Coleridge, Coleridge & Kidd (1964) and SCG was prepared in 0.9% w/v NaCl solution.

Results Recordings were obtained from 12 'C' fibre endings in 9 dogs. Conduction velocity was measured in 7 fibres and the mean was 3.1 m/s (s.e. mean ± 1.5 m/s). The fibres discharged spontaneously but the firing was irregular and sparse with, on average, 1 impulse occurring each second. All the endings increased their rate of discharge when capsaicin 10 μg/kg was given i.v. Ten minutes after SCG 100 μg/kg had been given i.v. the response of the fibres to capsaicin was reduced (Figure 1). In several experiments where repeated doses of capsaicin (10 μg/kg i.v.) were given at 15 min intervals the fibres remained refractory to capsaicin for approx. 45 min after administration of SCG. If a further dose of SCG was given after this time the fibre was again inhibited in its response to capsaicin. SCG did not affect the resting discharge of the 12 receptors.

The mean resting value for total lung resistance was 0.2 ± 0.05 kPa l^{-1}s and the mean resting value for dynamic lung compliance was 418 ± 48 ml kPa^{-1}. These values were unaffected by capsaicin (10 μg/kg i.v.) or SCG (100 μg/kg i.v.).

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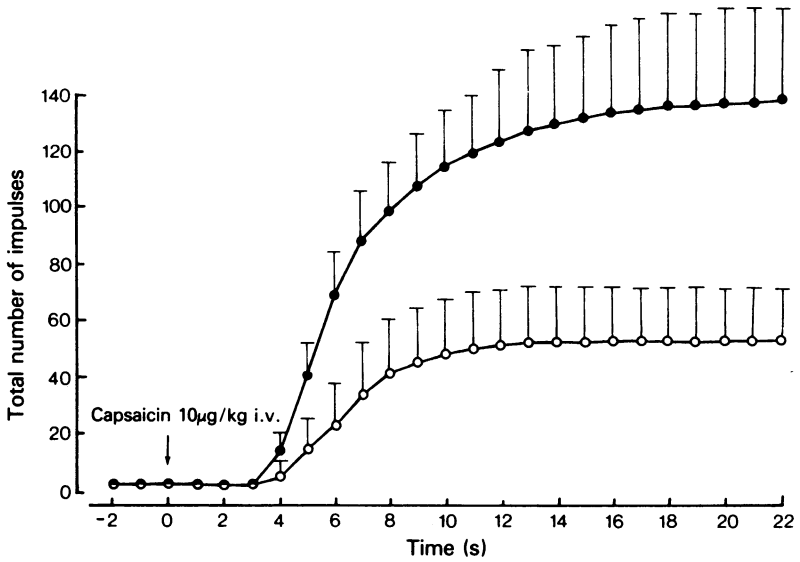

Figure 1 The effect of capsaicin (10 μg/kg i.v.) before (●) and 10 min after (○) treatment with sodium cromoglycate (100 μg/kg i.v.) on the rate of discharge of 12 'C' fibre endings in the dog lung. Each point represents the sum of the number of impulses occurring from time −2 s. Bars are s.e. mean.

Discussion SCG (100 μg/kg i.v.) suppressed the response of sensory 'C' fibre endings in the dog lung to capsaicin (10 μg/kg i.v.). Russel & Lai-Fook (1980) have shown that in dogs capsaicin (20 μg/kg i.v.) produced a vagally mediated bronchoconstriction, which they suggested resulted from stimulation of 'C' fibre endings in the lung. It is possible, therefore, that SCG could inhibit reflex bronchoconstrictor responses arising from 'C' fibre stimulation.

Unlike the lung 'irritant' receptors (Widdicombe, 1954) 'C' fibre endings do not respond well to mechanical distortion but they do respond to particular chemicals. Histamine, prostaglandins ($PGF_{2\alpha}$, PGE_1 and PGE_2), prostaglandin endoperoxide analogues, veratrum alkaloids and capsaicin all increase their rate of discharge (Coleridge, Coleridge, Ginzel, Baker, Banzett & Morrison, 1976; Ginzel, Morrison, Baker, Coleridge & Coleridge, 1978). Two of these substances, histamine and prostaglandin $F_{2\alpha}$ have been linked with the reflex changes in lung mechanics seen during asthmatic attacks (Piper & Vane, 1971).

Experiments in man have established the presence of sensory receptors in the lung which may be likened to the 'C' fibre endings (Jain, Subramanian, Julka & Guz, 1972). However, these receptors have yet to be assigned a physiological role in either the normal or asthmatic lung. If activation of 'C' fibre endings did initiate bronchoconstriction in the asthmatic lung then the prophylactic effectiveness of SCG in certain types of asthmatic bronchoconstriction involving a reflex may be explained, at least in part, by a neurophysiological action.

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