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Inhibitory effect of sodium cromoglycate on pulmonary responses to histamine administered after indomethacin in anaesthetized guinea-pigs

H.W. Mitchell

Department of Physiology, University of Western Australia, Nedlands 6009, Australia

1 Histamine (2–4 $\mu g\,kg^{-1}$ i.v.) increased airways resistance (R_{aw}) and decreased dynamic lung compliance (C_{dyn}) in urethane-anaesthetized guinea-pigs. The effects on R_{aw} were almost abolished by atropine (0.1 $mg\,kg^{-1}$ i.v.) and reduced by vagal cooling (11–16°C).

2 Histamine-induced changes in R_{aw} and C_{dyn} were significantly ($P < 0.05$) enhanced by indomethacin (1 $mg\,kg^{-1}$ i.v.).

3 In animals not treated with indomethacin, exposure to an aerosol containing sodium cromoglycate (0.01–2% for 30 s) failed to affect subsequent (3 min) histamine-induced bronchoconstriction.

4 Administration of an aerosol containing low (0.01–0.2%) concentrations of sodium cromoglycate had no effect on the enhanced responses (i.e. hyperreactivity) seen after indomethacin. However, more concentrated sodium cromoglycate aerosols (>0.2%) reduced or abolished the hyperreactivity to histamine seen after indomethacin.

5 It was concluded that sodium cromoglycate can prevent the development of hyperreactivity to histamine, possibly by interacting with some mechanism utilized by both histamine and indomethacin in this model.

Introduction

The non-steroidal anti-inflammatory drug (NSAID), indomethacin, has been shown to affect lung function in several different circumstances or conditions. In man indomethacin exacerbates asthma in a proportion of asthmatic adults and children (i.e. aspirin-intolerant patients) and it enhances bronchial responsiveness to antigen in non-asthmatic people with rhinitis (Fish *et al.*, 1981). This drug also reduces the refractory period commonly seen after exercise-induced asthma (O'Byrne & Jones, 1986). The mechanisms are not understood although inhibition of eicosanoid metabolism (Szczeklik *et al.*, 1977) and altered neuroeffector transmission (Ito & Tajima, 1981) have been suggested to account for some effects.

In animals indomethacin enhances responsiveness (reactivity) of the lungs to histamine, 5-HT (Mitchell, 1983; Mitchell & Adcock, 1988) and acetylcholine after O_3 (Murlas *et al.*, 1986). In guinea-pig lungs the increased airways response (measured as increased airways resistance) to histamine evoked by indomethacin can also be induced by aspirin, flufenamate and phenylbutazone (Mitchell & Adcock, 1987). The mechanism is unclear although preliminary evidence suggests that the hyperreactivity depends on the integrity of the vagus nerves (Mitchell & Adcock, 1988) suggesting that indomethacin may interact with histamine-activated bronchomotor reflexes.

Because there are some similarities between the effects of NSAIDs in aspirin-intolerant patients and in the guinea-pig model (e.g. in the sensitivity to different NSAIDs), it was decided to investigate the effects of sodium cromoglycate on the bronchial hyperreactivity induced by indomethacin in animals. Sodium cromoglycate has been found to be useful in the clinical treatment of some, but not all, aspirin-intolerant patients (Basomba *et al.*, 1976; Delaney, 1976; Dahl, 1981).

Sodium cromoglycate inhibits mediator release or mast cell disruption after antigen challenge (Goose & Blair, 1969; Farmer *et al.*, 1973) and it may antagonize the effects of platelet activating factor (Basran *et al.*, 1983). Furthermore, sensory nerve activity appears to be inhibited in animals (Dixon *et al.*, 1980) and possibly in man (Collier & Fuller, 1983). These putative effects of sodium cromoglycate

on sensory nerves may partly account for the inhibition of responses to bronchoconstrictor drugs found in dogs (Jackson & Richards, 1977a) and children (Woenne *et al.*, 1979) after inhalation of an aerosol containing 1–2% sodium cromoglycate.

The present results demonstrate a further novel effect of sodium cromoglycate since it appears to inhibit or abolish indomethacin-induced hyperreactivity to histamine in the anaesthetized guinea-pig.

Methods

Guinea-pigs weighing between 300–350 g were used in these experiments. Animals were anaesthetized with 1.25–1.5 g kg^{-1} i.p. urethane and they were kept warm (37.5 ± 0.2°C) with a thermostatically controlled heating blanket. Airways resistance (R_{aw}) and dynamic compliance (C_{dyn}) were calculated from the airflow, intrapleural pressure and tidal volume in spontaneously respiring animals. Animal preparation was the same as previously described (Mitchell, 1983; Nayler & Mitchell, 1987) except that a wider catheter (2 mm i.d.) was used in most experiments for recording the intrapleural pressure. R_{aw} and C_{dyn} were determined using an Apple 11e microcomputer. R_{aw} was calculated as pressure divided by flow at half tidal volume (obtained by integration of flow utilizing the computer software), whereas C_{dyn} was calculated from volume divided by pressure at zero flow. In some experiments blood pressure was monitored from a cannula placed in a common carotid artery.

Pulmonary responses were recorded breath-by-breath as changes in R_{aw} and C_{dyn} and, in some experiments by determining ventilation ($\dot{V}_I$), respiratory frequency (f) and changes in end-expiratory volume (change in FRC). Responses to histamine (i.v.) producing 50–100% increases in R_{aw} were obtained by varying the dose, usually between 2–4 $\mu g\,kg^{-1}$. Generally respiration was monitored for at least 5 control breathing cycles before injection of histamine. Actual R_{aw} and C_{dyn} responses to histamine were then determined before and after indomethacin (10–45 min) or sodium cromoglycate.

The pulmonary responses to low doses of histamine were mediated partially via vagal mechanisms (see Results). To demonstrate the vagal component of the responses some experiments were carried out in animals with cooled vagi or after the intravenous injection of atropine. Cervical vagosympathetic nerves were cooled by placing both nerve trunks on brass thermodes through which cold (−20°C) ethanol/water mixture was circulated. Temperature at the nerve surface was recorded with a thermocouple. The thermodes, thermocouple and nerves were sealed in 4% agar to reduce drying and thermal gradients (Franz & Iggo, 1968). The nerves were rapidly cooled, over a 30 s period to 11–16°C and a histamine response was recorded after which the vagi were allowed to rewarm. The effect of cooling on vagal conduction was tested by stimulating the vagus through the 'block' with d.c. square wave pulses of 0.5 ms duration and 10–20 Hz frequency.

Sodium cromoglycate was administered to the lungs by aerosol using the system described previously (Nayler & Mitchell, 1987). Animals' heads were placed in a perspex box into which the aerosol was generated. By operating a valve, which was connected to a 3-way tracheal cannula, animals inspired from the box containing the vapour for a predetermined period (30 s) before being returned to room air ventilation. Vapour deposits tended to condense within the tracheal cannula increasing basal R_{aw}, therefore the cannula was suctioned after each exposure to minimize this effect. Vapour was generated by an Inspiron MiniNeb nebulizer at a flow rate of 10 l min^{-1}; 0.27 ml drug solution is vapourized under these conditions in one min enabling vapour concentration to be calculated, e.g. at 0.0028 $\mu g\,ml^{-1}$ for a 0.01% w/v solution of sodium cromoglycate or 0.54 $\mu g\,ml^{-1}$ for 2% sodium cromoglycate. Thus, assuming $\dot{V}_I$ to be 100 ml min^{-1} (see Results), the inspired dose of sodium cromoglycate was 0.14 μg and 28 μg, respectively for the two examples given above.

The effect of sodium cromoglycate and indomethacin on pulmonary responsiveness was investigated by recording bronchoconstrictor responses (increases in R_{aw} and decreases in C_{dyn}) to histamine 15 min before and 3 min after the start of a 30 s delivery of sodium cromoglycate aerosol. At least 15 min was permitted between histamine doses. Generally duplicate histamine responses were obtained in the absence and presence of sodium cromoglycate. Indomethacin (1 mg kg^{-1} i.v.) was then administered and the histamine responses (3 min after sodium cromoglycate aerosol) determined in duplicate or triplicate again.

Drugs and statistics

Histamine acid phosphate, atropine sulphate and indomethacin were obtained from Sigma Chemicals. Histamine and atropine were prepared in 0.9% w/v NaCl solution (saline) and indomethacin was made up in 100 mM Na_2CO_3 solution. Pure sodium cromoglycate was obtained from Intal Spincaps and it was prepared in saline.

Statistical evaluation was carried out on paired data by comparing basal values or histamine-induced responses before and after exposure to sodium cromoglycate or indomethacin in each

Table 1 Effect of sodium cromoglycate (SCG) on bronchoconstrictor responses to histamine

		Control ($n = 13$)	*SCG 0.01%* ($n = 4$)	*SCG 0.2–0.4%* ($n = 5$)	*SCG 2%* ($n = 4$)
$\dot{V}_I$	Basal (ml min^{-1})	107 ± 7	95 ± 5	103 ± 9	118 ± 12
	Decrease (%)	19 ± 6	10 ± 6	13 ± 10	18 ± 12
f	Basal (breaths min^{-1})	80 ± 5	57 ± 6	88 ± 10	79 ± 10
	Increase (%)	53 ± 7	34 ± 5¶	49 ± 4¶	95 ± 65
Δ FRC	Increase (ml)	0.8 ± 0.2	0.3 ± 0.1	1.5 ± 0.8	1.2 ± 1.2
R_{aw}	Basal (cmH_2O ml s^{-1})	0.30 ± 0.04	0.30 ± 0.03	0.33 ± 0.09	0.15 ± 0.05†
	Increase (%)	75 ± 13	76 ± 19	100 ± 35	59 ± 29
C_{dyn}	Basal (ml cmH_2O^{-1})	0.55 ± 0.14	0.96 ± 0.23	1.06 ± 0.22	0.24 ± 0.04†
	Decrease (%)	32 ± 6	47 ± 12	32 ± 9	33 ± 17

Basal breathing pattern in anaesthetized guinea-pigs and changes (in some parameters) evoked by 2–4 μg kg^{-1} i.v. histamine. Results are mean ± s.e. mean. The table shows combined control (i.e. without prior exposure to SCG) and test (i.e. 3 min after exposure to SCG aerosol) data. † Not significantly different from appropriate controls (airways resistance (R_{aw}) = 0.20 ± 0.03 cmH_2O ml s^{-1} and dynamic lung compliance (C_{dyn}) = 0.26 ± 0.03 ml cmH_2O^{-1}). ¶ $P < 0.02$, mean difference in paired responses (i.e. before and after SCG). n, number of animals. $\dot{V}_I$ = ventilation, f = respiratory frequency and FRC = end-expiratory volume.

animal. These comparisons were carried out by use of Student's paired t test and $P < 0.05$ was assumed to represent a significant difference between means or between the paired bronchoconstrictor responses. The data shown are the mean ± s.e. mean.

Results

Intravenous injections of histamine produced a transient tachypnoea, an increase in FRC, an increase in R_{aw} and a decrease in C_{dyn} (Table 1 and Figure 2). Ventilation ($\dot{V}_I$) usually increased for a few breaths after injecting histamine (~5 breaths) but thereafter it fell for 30 s–1 min.

Effect of atropine and vagal cooling on responses to histamine

Increases in R_{aw} induced by low doses of histamine (2–4 μg kg^{-1} i.v.) were markedly reduced by atropine (0.1 mg kg^{-1} i.v.). The atropine effect was rapid, prolonged and ranged from 50–>90% inhibition. An example of data from one such experiment is shown in Figure 1. The results shown were representative of three experiments (animals).

Similarly, vagal cooling reduced histamine-induced increases in R_{aw}. As the vagi were cooled, respiratory frequency declined and became deeper. There were few, if any differences in breathing pattern if the vagi were cooled beyond 11–16°C. Cardiac responses to electrical stimulation of the efferent vagus (bradycardia) were not blocked at these temperatures. However, the histamine-induced increase in R_{aw} was reduced by 51 ± 21% ($n = 5$).

Effect of sodium cromoglycate on responses to histamine

Isotonic saline (0.9% w/v) aerosols had no effect on basal values or on evoked responses to histamine (3 experiments). Similarly, aerosol administration of sodium cromoglycate induced few changes, either pulmonary or cardiovascular (Table 1). The only consistent change in histamine responses observed was a modest fall in the magnitude of the tachypnoea seen after histamine administration. However,

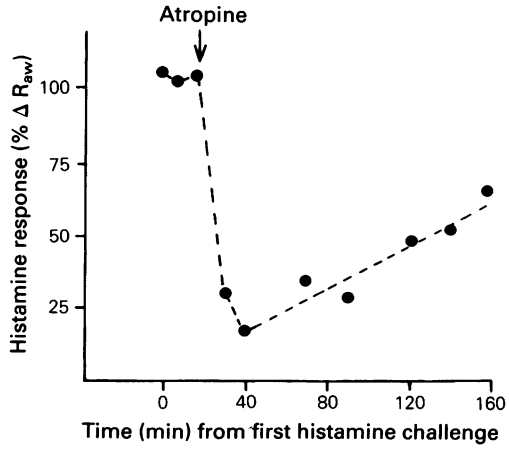

Figure 1 Time-course and effect of a single injection of atropine (0.1 mg kg^{-1} i.v.) on histamine-induced (3 μg kg^{-1} i.v.) increases in airways resistance (R_{aw}) in one anaesthetized guinea-pig. Histamine responses were inhibited by more than 80%.

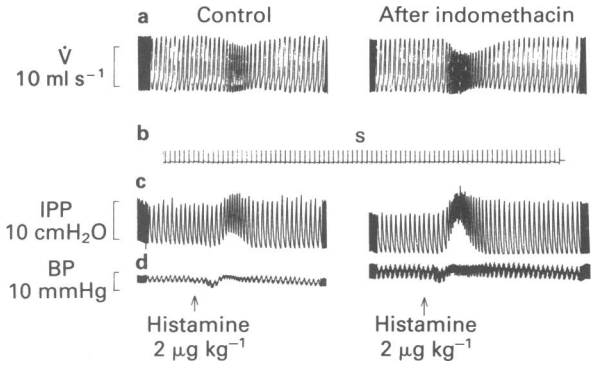

Figure 2 Records from a spontaneously respiring anaesthetized guinea-pig. The records show (a) airflow ($\dot{V}$), (b) time marker (s), (c) intrapleural pressure (IPP) and (d) arterial blood pressure (BP). No tidal volume data are shown because they were generated by the computer-based system. On respiratory traces inspiration is upwards. For blood pressure zero pressure (i.e. atmospheric pressure) is upwards. The mean arterial pressure was in the range 25–50 mmHg in different experiments. The records show the effect of histamine (2 $\mu g\,kg^{-1}$ i.v.) before and 30 min after injection of indomethacin (1 $mg\,kg^{-1}$ i.v.). Indomethacin increased the effect of histamine on airways resistance and on respiratory rate.

this apparent effect of sodium cromoglycate was not seen with the most concentrated (2%) aerosol used.

Effects of sodium cromoglycate on indomethacin-induced hyperreactivity to histamine

Indomethacin has been shown previously to increase consistently the R_{aw} responses to histamine (i.e. cause hyperreactivity) in the urethane-anaesthetized guinea-pig (Mitchell, 1983; Mitchell & Adcock, 1987). In the present experiments too, indomethacin (1 $mg\,kg^{-1}$) increased some of the pulmonary responses to histamine (Figure 2), e.g. causing a 72% increase in the R_{aw} response to histamine (Table 2). Basal R_{aw} and the increased FRC commonly seen after histamine were not altered by indomethacin, either in the presence or absence of sodium cromoglycate.

The effect of sodium cromoglycate on indomethacin-induced hyperreactivity is shown in Table 2. An aerosol containing a low concentration of sodium cromoglycate (0.01%) had no effect on indomethacin-induced increases in responses (increase in R_{aw}, decrease in C_{dyn}) to histamine. More concentrated aerosols of sodium cromoglycate, however, reduced or abolished the hyperreactivity. No differences were seen between the effects of 0.2% and 0.4% sodium cromoglycate, therefore the data are combined (also in Table 1). No further effects were observed using 2% sodium cromoglycate.

The inhibitory effect of high doses of sodium cromoglycate did not depend on its presence in the lung before the administration of indomethacin. Figure 3 shows an example of one experiment in which effective blockade of indomethacin-induced hyperreactivity was achieved by a brief exposure (30 s) to a 2% aerosol of sodium cromoglycate some 15 min after the onset of the indomethacin-induced hyperreactivity to histamine. Moreover, hyperreactivity was readily re-established 15 min later when the histamine-induced response was obtained without sodium cromoglycate exposure. Similarly, discontinuation of higher doses of sodium cromoglycate which inhibit indomethacin-induced hyperreactivity, resulted in enhanced increases in R_{aw} evoked by histamine (i.e. the re-emergence of hyperreactivity, $n = 3$).

Table 2 Effect of indomethacin on histamine-induced bronchoconstrictor responses

	n	ΔR_{aw} (%)	ΔC_{dyn} (%)
Control (no SCG)	3	+72 ± 16*	+48 ± 17*
SCG 0.01%	4	+71 ± 16*	+50 ± 79
0.2–0.4%	5	+11 ± 7	−9 ± 68
2%	4	+18 ± 18	+23 ± 48

Mean peak % changes in the increase in airways resistance (R_{aw}) and decrease in dynamic lung compliance (C_{dyn}) evoked by histamine (2–4 $\mu g\,kg^{-1}$ i.v.) are shown in the absence (control) of sodium cromoglycate (SCG) or 3 min after aerosol exposure to SCG. All the tabulated changes (in R_{aw} and C_{dyn} responses to histamine) were caused by the injection of indomethacin (1 $mg\,kg^{-1}$ i.v.). * $P < 0.05$ mean difference in paired responses (i.e. before and after indomethacin). *n*, number of animals.

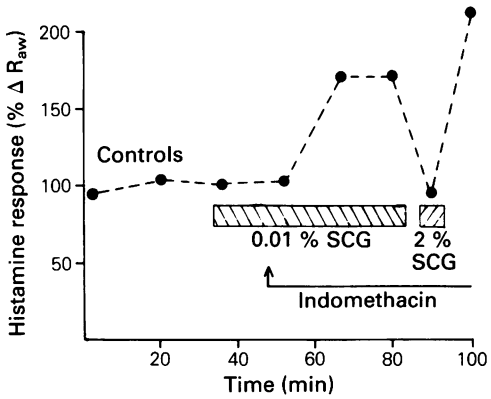

Figure 3 Effect of sodium cromoglycate (SCG) aerosol and indomethacin (1 mg kg^{-1} i.v.) on histamine-induced (3 $\mu g\,kg^{-1}$ i.v.) increases in airways resistance (R_{aw}) in an anaesthetized guinea-pig. Two control responses to histamine were obtained followed by one response 3 min after exposure to a low concentration (0.01%) of sodium cromoglycate (for 30 s). Sodium cromoglycate had no effect on the histamine response. After injection of indomethacin histamine responses (each recorded 3 min after sodium cromoglycate exposure) were increased. However, a single exposure to a higher concentration of sodium cromoglycate (2%) reversed the hyperreactivity to histamine. Hyperreactivity to histamine was then re-established by omitting sodium cromoglycate exposure.

Discussion

The results of this study indicate that whilst sodium cromoglycate aerosol has little effect on histamine-induced pulmonary responses it does prevent the development of hyperreactivity (e.g. increased responses of R_{aw} to histamine) after indomethacin. The possibility that exposure to a saline vapour may reduce bronchial reactivity was considered but no evidence for such an effect found (e.g. hyperreactivity was present despite exposure to low doses of sodium cromoglycate). Moreover, altered osmotic strength of drug aerosols was insignificant, e.g. the 0.2% solution had an osmotic strength of approximately 310 mosmol l^{-1}, whereas the most dilute solution had an osmotic strength of 300.6 mosmol l^{-1}. Sodium cromoglycate has been used prophylactically in patients with asthma and in the bronchospasm provoked by aspirin and other NSAIDs (Basomba *et al.*, 1976; Delaney, 1976). The anti-asthma mechanism of this drug is currently not known (Altuonyan, 1980; Richards *et al.*, 1986). Since neither the anti-asthma mechanism of this drug nor its mechanism in aspirin-intolerance are known, it is not possible to predict with any certainty how it may achieve the novel effect on indomethacin-induced hyperreactivity in guinea-pigs described in this study.

Sodium cromoglycate did not need to be administered before indomethacin to suppress the evoked hyperreactivity, but it was necessary for it to be delivered a short time before bronchoconstriction was induced (by histamine): a single exposure to aerosol was sufficient to reduce subsequent bronchoconstrictor responses to normal (i.e. control). In this respect the effects of sodium cromoglycate in guinea-pigs and man are similar. The duration of action of sodium cromoglycate was not directly measured. However, it can be inferred that its effect lasts less than 15 min, because enhanced bronchoconstrictor responses to histamine were obtained approximately 15 min after discontinuation of the sodium cromoglycate aerosol.

The possibility that sodium cromoglycate may interact with histamine and/or indomethacin at some reflex level was considered, because histamine-induced bronchoconstriction was largely reflex (see below) and the evidence indicates that the indomethacin effect is no longer present after vagotomy or vagal cooling (11–16°C, Mitchell & Adcock, 1988). Histamine may increase pulmonary impedance via vagal mechanisms in several species including dogs (Gold *et al.*, 1972; Jackson & Richards, 1977a), rabbits (Mills *et al.*, 1969) and guinea-pigs (Mills & Widdicombe, 1970). The extent of this reflex component varies with anaesthesia (Jackson & Richards, 1977b) and histamine dose. In asthmatic man bronchoconstriction may be inhibited by atropine (e.g. Boushey, 1980). In the present experiments the increased R_{aw} evoked by histamine (2–4 $\mu g\,kg^{-1}$) was >50% inhibited after low doses of atropine and after vagal cooling from which it appears that a substantial part of the response was reflex. The vagi were only cooled to 11–16°C because this was sufficient to initiate respiratory changes consistent with blockade of slow and rapidly adapting afferents whilst efferent conduction was not blocked (Franz & Iggo, 1968; Widdicombe, 1974). However, there was little evidence that sodium cromoglycate (to 2%) antagonized vagal or non-vagal responses in the guinea-pig, although histamine-induced tachypnoea was somewhat less after low and intermediate doses of sodium cromoglycate. Histamine-induced bronchoconstriction was not affected.

In the anaesthetized dog sodium cromoglycate aerosol (1–2%) reduces the vagally-dependent bronchoconstriction to histamine (Jackson & Richards, 1977a). Responses to electrical stimulation of the efferent vagus were not affected and it was suggested that sodium cromoglycate reduced activity of histamine sensitive vagal afferents. This was later supported by direct electrical recordings which demonstrated that sodium cromoglycate reduced

discharge from capsaicin-stimulated vagal afferents, possibly C-fibres (Dixon *et al.*, 1980). There thus appears to be important species differences in sensitivity to sodium cromoglycate, or histamine may activate different vagal pathways to initiate bronchoconstriction in the two species.

This paper describes a novel pharmacological action of sodium cromoglycate in that it inhibits hyperreactivity induced by indomethacin in the guinea-pig, possibly by acting at some common point of interaction of histamine and indomethacin which otherwise evokes enhanced bronchoconstriction.

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