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EVIDENCE FOR AN EFFECT OF SODIUM CROMOGLYCATE ON SENSORY NERVES IN MAN

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1 Sodium cromoglycate was given by both intravenous injection and local intra-arterial infusion to healthy volunteers.

2 Intravenous injection of a dose of 4 mg in four subjects caused a statistically significant rise in blood pressure and pulse rate associated with a feeling of warmth in the perineum and blush areas of the face and chest.

3 Brachial artery infusion of sodium cromoglycate at doses of 100–1000 μg/min caused a feeling of warmth in the limb during 26 out of 30 infusions and this sensation was subject to tachyphylaxis. During eight infusions in which there was a sensation of warmth there was no change in local blood flow as measured by strain-gauge plethysmography. In a further six studies involving 12 infusions of sodium cromoglycate the feeling of warmth was not accompanied by a rise in local skin temperature.

4 The results suggest that sodium cromoglycate may stimulate afferent nerves in man.

Keywords sodium cromoglycate sensory mechanisms

Introduction

Sodium cromoglycate, which is used for the treatment of asthma, is generally believed to act by preventing the release of bronchoconstrictor mediators from pulmonary mast cells (Cox *et al.*, 1970). However, since the drug is effective against challenges thought unlikely to involve the release of these mediators, such as bronchoconstriction produced by nebulised distilled water (Fuller & Collier, 1983) exercise (Davies, 1968) or the inhalation of cold air (Fanta *et al.*, 1981), mechanisms other than those that effect mast cells may contribute to its action.

Recently it has been suggested that cromoglycate might work by interfering with sensory mechanisms. In the dog sodium cromoglycate causes hypotension and bradycardia (Dixon *et al.*, 1979) and in the marmoset hypertension and tachycardia (Cox *et al.*, 1970); in both animals pharmacological and surgical manipulation suggested that these effects were secondary to stimulation of the sensory component of the autonomic nervous system. Furthermore in the dog measurement of impulse rates recorded from sensory nerves from the left ventricle gave direct evidence for such nervous stimulation (Dixon *et al.*, 1979). Tachyphylaxis developed to the stimulant effects of sodium cromoglycate in these studies and in unpublished observations this has been found to be associated with sensory nerve blockade (Jackson, 1982, personal communication), certainly the drug can block sensory input into non-myelinated (C-) fibres (Dixon *et al.*, 1980). If this blockade were to occur in patients with asthma it could account for the clinically observed capacity of the drug to prevent nervously induced bronchoconstriction. We report here the results of a study which supports the concept that the drug affects sensory nerves in man.

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Methods

Studies were performed in healthy volunteers of both sexes aged between 20–40 years old who gave their informed consent; approval for the study was given by the Ethical Committee of this hospital. During the study volunteers rested supine in a quiet laboratory. Ambient temperature varied from 22–25°C although in any one study it remained constant.

Intravenous (systemic) experiments

A 4 mg dose of sodium cromoglycate diluted in saline was infused over 1 min through a needle placed in a superficial vein in the arm. Blood pressure was measured directly via a needle (19swg) introduced into the brachial artery under local anaesthesia and connected by a catheter to a Statham pressure transducer linked to a Devices recorder. Heart rate and rhythm were recorded continuously from external

ECG limb leads connected to a Cambridge Monitor. Sensations observed by the subjects were reported as they occurred.

Intra-arterial (local) experiments

A dose of 100–1000 μg/min sodium cromoglycate diluted in normal saline (pH of all solutions was 5.0) was infused into the brachial artery of one arm through a short bevel (26 swg) unmounted needle, inserted under local anaesthesia, attached by a cannula to a Harvard Syringe Pump.

Blood flow through the forearm was measured by mercury-in-rubber strain-gauge plethysmography. Congestion was provided by a cuff around the upper arm inflated to 30 mm Hg for 10s in every 15s. Flow was recorded with the hand either in, or out of, the circulation, exclusion being achieved by inflating an arresting cuff around the wrist to a suprasystolic pressure of 200 mm Hg.

Sensation was assessed by an independent observer who was unaware of the nature of the infusate. The subject was asked at the end of each minute of infusion to describe any sensation that developed, comparing the feelings in the test arm with those in the control arm, and also comparing sensation in the test arm with that occurring during the previous infusion. Saline or sodium cromoglycate were infused in 4 min cycles in an order determined by the second investigator.

Skin temperature

In six subjects the effect of sodium cromoglycate on skin temperature was measured by thermocouples applied to the skin on the back of each hand. Temperature, and the subject's assessment of warmth, were recorded at the end of each infusion.

Results

Intravenous (systemic) experiments

Sensation Within 15 s of completing the cromoglycate infusion all four subjects noticed a warm sensation which started in the perineum and in three spread to involve the blush areas of the chest, face and neck. Intensity of sensation reached a peak within a minute of its first being felt and waned over the subsequent 4 min. Intensity varied from subject-to-subject, so that in three the peak sensation was deemed painful while in the fourth it was mild. During symptoms there was no apparent change in skin colour in those blush areas observed, i.e. face, neck and upper chest.

Blood pressure. Mean blood pressure (± 1 s.d.) prior to sodium cromoglycate was 108 ± 6 mm Hg systolic and 71 ± 12 mm Hg diastolic. In all subjects pressure rose after sodium cromoglycate and reached a peak 1 min after the end of the infusion (Figure 1). The mean rise was 20 ± 5.4 mm Hg for systolic pressure and 10 ± 2 mm Hg for diastolic pressure. The pressure then fell and by the tenth minute was similar to control. Analysis by paired *t*-test showed that for both systolic and diastolic pressures the rise was statistically significant ($P = 0.05$).

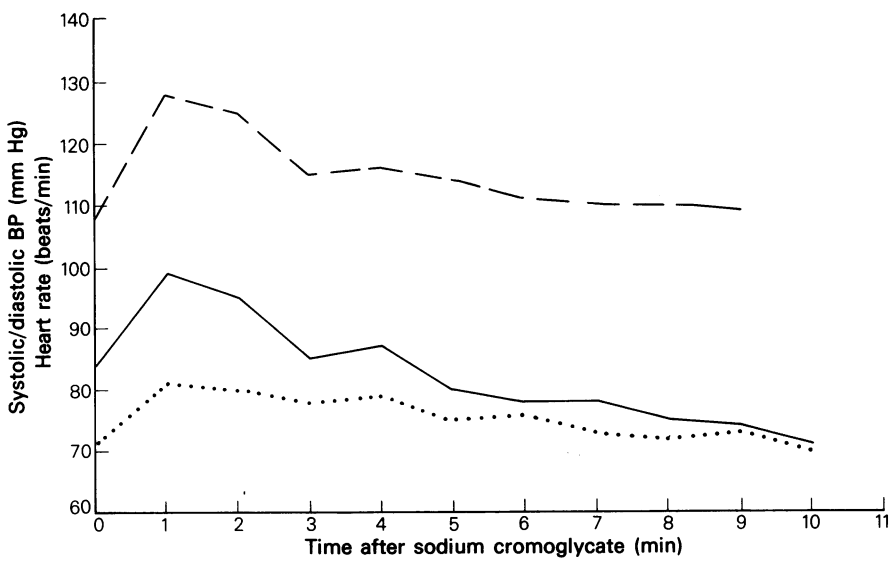

Figure 1 The effect of an i.v. injection of 4 mg of sodium cromoglycate (given over 1 min starting at time 0) on heart rate (——), diastolic pressure (.....) and systolic pressure (—), in four subjects. The mean rise in heart rate, systolic pressure and diastolic pressure were statistically significant using the paired *t*-test.

Heart rate. Mean heart rate (± 1s.d.) before the drug was infused was 84 ± 29 beats/min. Following infusion, the mean rise in heart rate was plus 15 ± 2.4 beats/min, and reached a mean peak of 99 ± 32 beats/min at 1 min. Analysis using the paired *t*-test showed that the rise was statistically significant ($P < 0.01$). By the fifth minute after the end of the infusion heart rate had fallen to below pre-drug levels. During the period of the peak heart rate subjects were aware of an increased force of their heart beat. No change in ventricular ectopic rate was seen during or after the drug infusion.

Intra-arterial (local) experiments

Sensation. In 17 out of 21 *initial* challenges in 14 subjects infusions of sodium cromoglycate into the brachial artery at a dose of 100 μg/min over 4 min caused a sensation of warmth in the limb. The burning sensation was also noted on all nine occasions when SCG was infused at 1000 μg/min. The sensation was analysed in detail by infusing different doses of the drug and interspersing these with infusions of saline in three subjects. In these studies the initial challenge with cromoglycate at 100 μg/min caused a burning sensation that developed within 30s of starting the drug, reached a maximum at about 1 min, continued throughout the duration of the infusion and had disappeared 1–2 min after stopping the drug. When the same dose was given a second or third time the sensation was less intense. Intensity similar to that reported during the initial infusion was achieved only when the dose of drug was greatly increased (in two subjects to 1000 μg/min over 4 min and, in the third to 500 μg/min over 4 min). The sensation caused during these initial challenge infusions at 100 μg/min was identified as different from that caused by saline on six out of seven occasions (see Figure 2). After the higher dose, *subsequent* infusion at 100 μg/min was only identified as being different from saline in one out of ten challenges; there was therefore a significant reduction in the ability of the subjects to correctly identify the nature of the infusion ($P = 0.016$ Fisher's Exact test). Furthermore a second infusion at the higher dose produced a diminished response when compared to the first infusion at that dose.

In seven subjects the larger i.a. dose (1000 μg for 4 min) also produced a warm sensation in the face and neck. In all subjects when the dose was repeated the response to the second infusion was less than that to the first. In none of the studies in which there was a sensation of warmth was there any noticeable change in local skin colour.

Blood flow. In four subjects blood flow through the

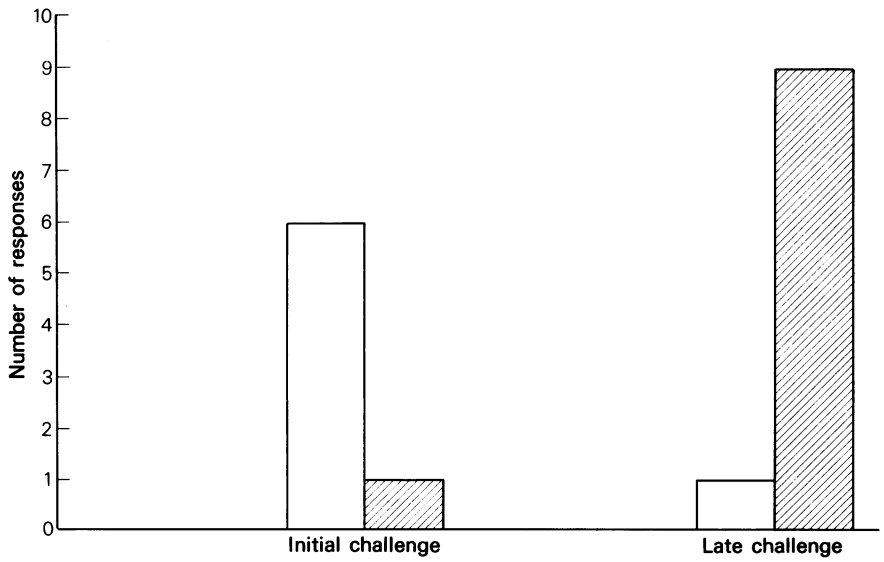

Figure 2 The figure shows the number of occasions when a challenge with local intra-arterial infusion of sodium cromoglycate (100 μg/min for 4 min) caused a feeling of warmth; a 'positive response' (□) indicates the feeling was distinguishable from saline, a 'negative response' (▨) indicates the feeling was indistinguishable from saline. The columns on the left show responses to the initial 100 μg/min challenge, those on the right the responses to later challenges by the same dose but given after the subject had received a 4 min infusion of sodium cromoglycate at the higher dose of 500 μg–1000 μg/min. The difference between the number of positive and negative response before and after the interspersed high dose of SCG was statistically significant ($P < 0.02$) by the Fisher's Exact test.

forearm was measured during the local i.a. infusion of sodium cromoglycate (100 μg/min) while there was a typical feeling of warmth. In four studies the hand was isolated so that only forearm blood flow was measured. In a further four studies the hand was included in the circulation, so that measurements of blood flow through the forearm reflected the sum of the flow through the forearm plus the hand. When the hand was included flow through the forearm was 2.19 ± 0.5 ml 100 ml^{-1} min^{-1} during saline infusion and 2.15 ± 0.3 ml 100 ml^{-1} min^{-1} during the infusion of sodium cromoglycate (Figure 3). With the hand excluded flow through the forearm was 1.8 ± 0.2 ml 100 ml^{-1} min^{-1} on saline, and 1.5 ± 0.3 ml 100 ml^{-1} min^{-1} on sodium cromoglycate. These small reductions in flow were not significant since in both groups a fall of similar magnitude occurred in the contralateral (control) arm.

Skin temperature

During 12 infusions of sodium cromoglycate in which the subjects reported a feeling of warmth, skin temperatures on the back of the hand receiving sodium cromoglycate fell by 0.55 ± 0.94°C; and there was a similar fall of 0.53 ± 0.89°C in the control arm. During these studies room temperature was held constant at 23.0°C.

Discussion

The results of this study show that sodium cromoglycate causes a sensation of warmth or burning in the perineum, chest, face and neck after large (systemic) doses (2.4 mg or above), and that similar feelings restricted to the hand and forearm occur after local brachial artery infusions at the smaller but local dose of 100 μg/min. The plasma concentration associated with systemic symptoms was 400–1000 ng/ml (Fuller & Collier, 1983), while the plasma concentration required to produce a sensation in the hand and forearm was approximately 10 μg/ml (calculated by dividing the given dose by the forearm flow). There is therefore a different threshold for the sensation in different parts of the body. The systemic effects are similar to those observed by previous workers (Walker *et al.*, 1972). However, in this earlier report they were considered to be due to an increase in local skin temperature and therefore presumably attributed to an increase in local skin blood flow although local blood flow was not measured. In the present study no change was seen in skin colour or skin temperature. Similarly there was no evidence of an increase in blood flow through muscle (the predominant bed in the forearm) or through the skin (the predominant bed in the hand) when these were studied by plethysmography. The most likely explanation for the sensation is therefore that the drug acts by stimulating sensory nerves.

Stimulation of receptors on sensory nerves might also account for the increase in blood pressure and heart rate seen in this study. The drug has been reported to stimulate sensory nerves in the dog following its application to the endocardium (Dixon *et al.*, 1979), and in the marmoset (Cox *et al.*, 1970) where a

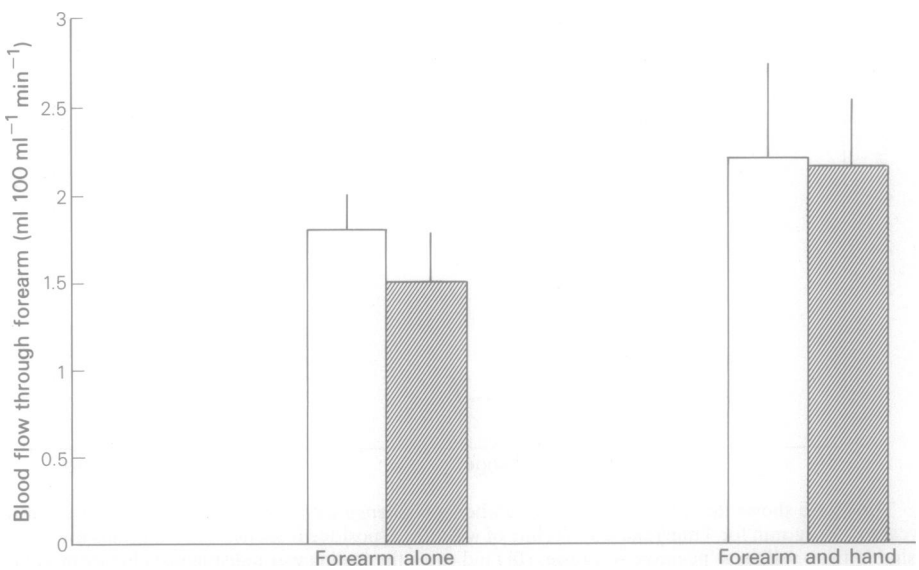

Figure 3 The effect of local infusion of sodium cromoglycate (100 μg/min for 4 min) on blood flow through the forearm (ml 100 ml^{-1} min^{-1}) with the hand in (four studies; forearm + hand), or out of (four studies; forearm alone), the circulation; measurements were made at a time when subjects reported a feeling of limb warmth. The columns give the mean ± 1 s.d. □ saline, ▨ sodium cromoglycate.

similar haemodynamic response (hypertension and tachycardia) occurs, the evidence is consistent with it being due to cardiac receptor stimulation. Furthermore it seemed unlikely that the response in man is secondary to changes in peripheral resistance in view of the lack of change in blood flow seen when the drug is given locally over a wide range of concentrations.

The plasma concentrations of sodium cromoglycate achieved in this study were in excess of those that would occur in plasma when the drug is used in normal therapeutic amounts. However the concentrations of sodium cromoglycate which would be achieved in the mucosae of the lung immediately after inhalation and as particles of the drug come in contact with the endothelial surface would also be very high. The initial effect of such concentrations in the lung might be to cause stimulation and this could account for the cough often seen when the drug is first inhaled. If stimulation were to be followed by blockade this would then also account for prevention of bronchocontsriction caused by sensory nerve stimulation. In the present study the development of tachyphylaxis to sensory stimulation infers that at least one type of blockade occurs following exposure to cromoglycate. In animal studies tachyphylaxis is associated with blockade (Jackson, 1982, personal communication) and blockade by sodium cromoglycate of C-fibre stimulation by capsaicin has also been reported (Dixon *et al.*, 1980). These C-fibres are known to occur in the airways of man where they contribute at least to cough (Collier & Fuller, 1982) and in dogs where their stimulation mediates bronchoconstriction (Russel & Lai-Fook, 1980). The evidence presented in this paper suggests that sodium cromoglycate can stimulate sensory nerves in man, and as such has actions other than that of inhibiting the release of mediators from mast cells. The mechanism by which cromoglycate works in asthma now needs further evaluation.

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